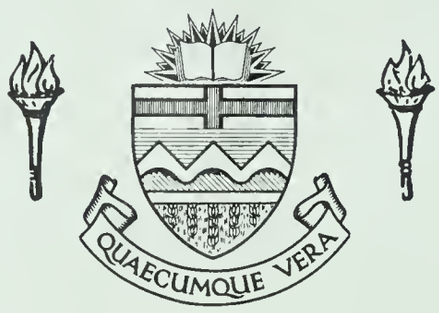

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THE UNIVERSITY OF ALBERTA

THE REACTION OF BENZHYDROL WITH SOME N^1-MONOSUBSTITUTED SULFANILAMIDES AND RELATED COMPOUNDS

BY

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A THESIS

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled "The Reaction of Benzhydrol with Some N^1-Monosubstituted Sulfanilamides and Related Compounds" submitted by Jerry Larry Malicky in partial fulfilment of requirements for the degree of Master of Science.

ABSTRACT

Sulfanilamides were found to undergo alkylation with benzhydrol, yielding either mono, di, or tribenzhydryl derivatives. Studies on model compounds, qualitative reactions and spectroscopic characteristics were employed in the elucidation of the structures of these reaction products. Sulfanilamide itself afforded a mono, a di, and two different trisubstituted derivatives, depending on the reaction conditions employed. The sequence of reactions leading to each of the products have been determined. One of the steps involves an intramolecular rearrangement of a benzhydryl radical. The benzhydrylsulfanilamides were found to be stable crystalline compounds, readily prepared and easily purified. Their melting points are such that these derivatives are most suitable for the identification and differentiation of the bacteriostatic sulfanilamides. The benzhydrylsulfanilamides were tested for inhibitory action on microorganisms. No inhibitory activity was found for either Escherichia coli or Staphylococcus aureus.

ACKNOWLEDGEMENTS

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INTRODUCTION

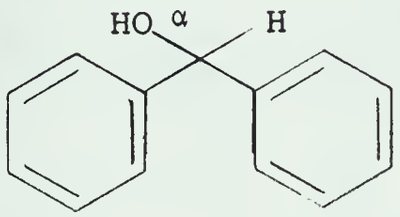
The Problem

Previous work in this laboratory revealed that sulfanilamides condensed readily with xanthydrol to yield the corresponding mono or dixanthenylsulfanilamides (1). These compounds, however, were very unstable towards heat, peroxides, and possibly other factors, creating great difficulties in attempts at obtaining pure samples. This fact, coupled with the considerable overlap that existed in their melting points severely limited the utility of this alcohol as a reagent for the characterization of the bacteriostatic sulfanilamides.

The present work was undertaken in the hope that a different alkylating agent could be found which might overcome the disadvantages observed with xanthydrol and thus offer a practical utility to alkyl derivatives for the identification and differentiation of the sulfanilamides.

LITERATURE SURVEY

Benzhydrol (I), also known as benzohydrol or diphenylcarbinol, is a relatively reactive secondary alcohol.



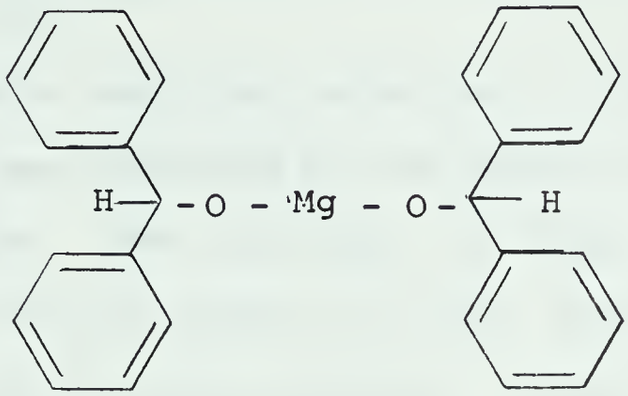
I

Physically, it is a white solid melting at 69°. It is freely soluble in organic solvents such as alcohol, ether, chloroform and carbon disulfide, but only sparingly soluble in water.

It is readily prepared by reduction of the corresponding ketone, namely benzophenone. Reducing agents which have been successfully employed for this purpose include: silicate borohydride or sodium borohydride (2), lithium borohydride (3), sodium triethoxy aluminum hydride (4), aluminum isopropylate in methanol (5), aluminum isopropoxide in isopropyl alcohol (6), t-butyl alcohol, t-butoxide with a high pressure of hydrogen (7), bimagnesium plumbide and sodium hydroxide in alcohol (8), sodium diethyl aluminum dihydride or sodium triisobutyl aluminum hydride (9).

The normal course of the reaction between isopropyl magnesium chloride and benzophenone should yield diphenylisopropylcarbinol. However, it was found that benzhydrol was

produced in significant amounts in the above reaction. It was postulated that the magnesium tetraphenyl ketyl (II) was formed under the conditions of the reaction.



II

When decomposed with water, it produced benzhydrol and the starting ketone (10).

Similarly, cyclohexylmagnesium bromide or cyclohexylmagnesium iodide, on reaction with benzophenone, afforded about a 6% yield of benzhydrol. This was likewise presumed to result from the intermediate ketyl (11). Ethyl benzoate also produced benzhydrol in moderate yields when treated with t-butylmagnesium chloride. It was postulated that benzophenone was formed as the intermediate, and that it was reduced to the alcohol under the conditions of the reaction (12). Benzoic acid, when condensed with t-butylmagnesium chloride, also produced moderate yields of benzhydrol (13).

Diphenylformamide, on reaction with phenylmagnesium bromide, was found to produce high yields of benzhydrol (14). As opposed to the reactions of Grignard reagents with carbonyl compounds, the aforementioned reaction with a disubstituted

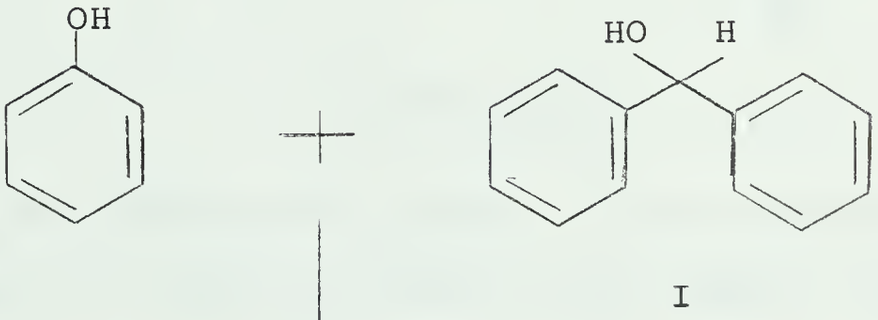
amide proceeds in a sufficiently high yield to be of value as a preparative procedure. Benzhydrol has also been obtained in high yields by simply refluxing triphenylgallium and benzaldehyde in benzene (15).

Besides methods involving reduction of the ketone, this alcohol has also been obtained by the oxidation of the corresponding hydrocarbon. Hock and Long (16) found that shaking diphenylmethane with dry oxygen for sixty hours under a mercury vapor lamp produced the hydroperoxide; on rapid heating benzhydrol was formed almost quantitatively.

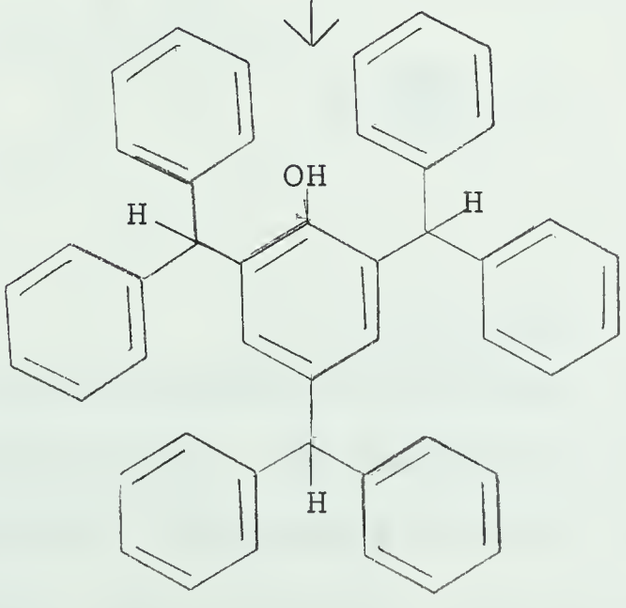
Although xanthydrol can form the corresponding xanthenyl cation in glacial acetic acid, benzhydrol (as well as triphenylcarbinol), is sufficiently less basic that a strong acid is necessary to produce the corresponding carbonium ion at a concentration great enough to yield an observable reaction rate (17). Bethell and Gold (18) studied the interconversion of benzhydrol to the acetate, and found that it was only rapid when an acid catalyst was used. Benzhydrol could be recovered from its acetic acid solution unchanged when a strong acid was absent. As one would expect, benzhydrol has been shown to be less reactive than xanthydrol (17, 19, 20) or triphenylcarbinol (17). However, benzhydrol has been demonstrated to be more reactive than either benzyl alcohol (21), methylphenylcarbinol or ethylphenylcarbinol (22). The benzhydryl carbonium ion is readily formed in concentrated sulfuric acid as indicated by the rapid development of a reddish-brown color in the solution (23).

In view of its reactivity, benzhydrol has been employed as an alkylating agent with a large variety of molecules possessing hydrogen substituted carbon, nitrogen, oxygen, and sulfur atoms.

Substitution at carbon occurs readily with compounds possessing an active aromatic ring. Shorigin (24) studied the reaction of benzhydrol with a number of phenols. Treatment of phenol itself, with an excess of benzhydrol, yielded the 2,4,6-trisubstituted product (III).

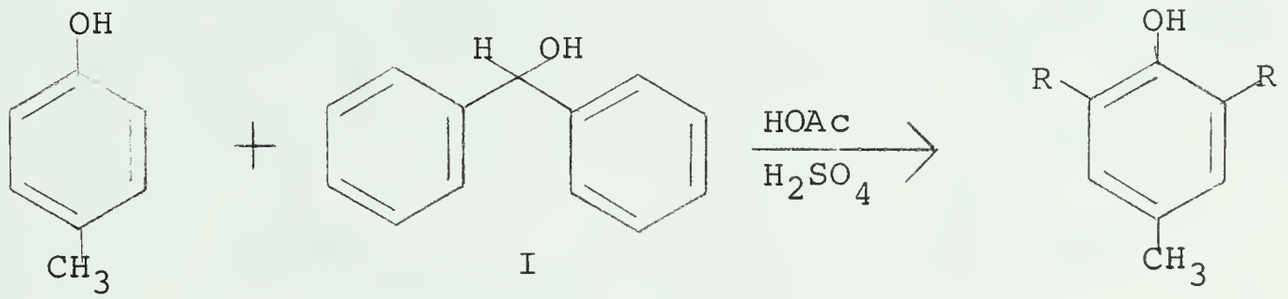


I



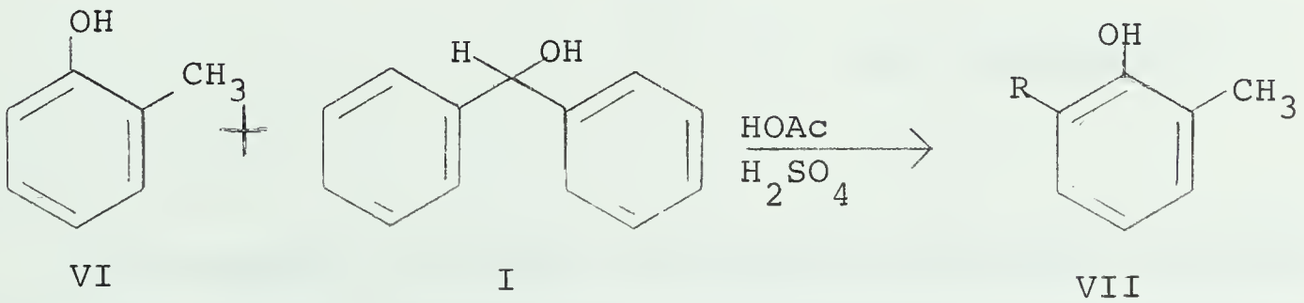
III

Compound III has also been prepared by Burton and Cheeseman (25) using 72% perchloric acid as the catalyst in a nitromethane solvent. These authors felt that their procedure was a decided improvement over that employed by Shorigin. When the para position is occupied, as in p-cresol (IV), the corresponding 2,6-disubstituted product (V) was recovered (24).



IV I (R = benzhydryl) V

o-Cresol (VI), on the other hand, afforded a monosubstituted product postulated to be the ortho substituted isomer (VII).

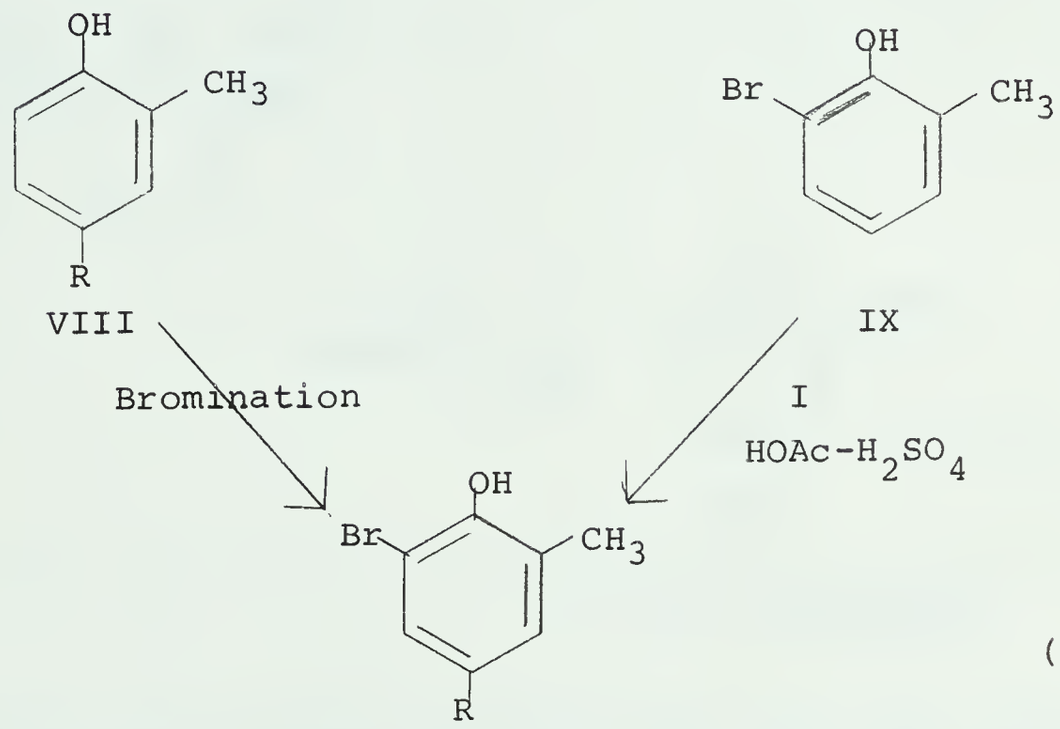


VI I VII

(R = benzhydryl)

Since this latter structural assignment was not in any way confirmed, Iddles et al. (26) undertook a more detailed study of this reaction. By heating VI with I in an acetic-sulfuric acid medium, they recovered a product having a melting point identical to that reported by Shorigin.

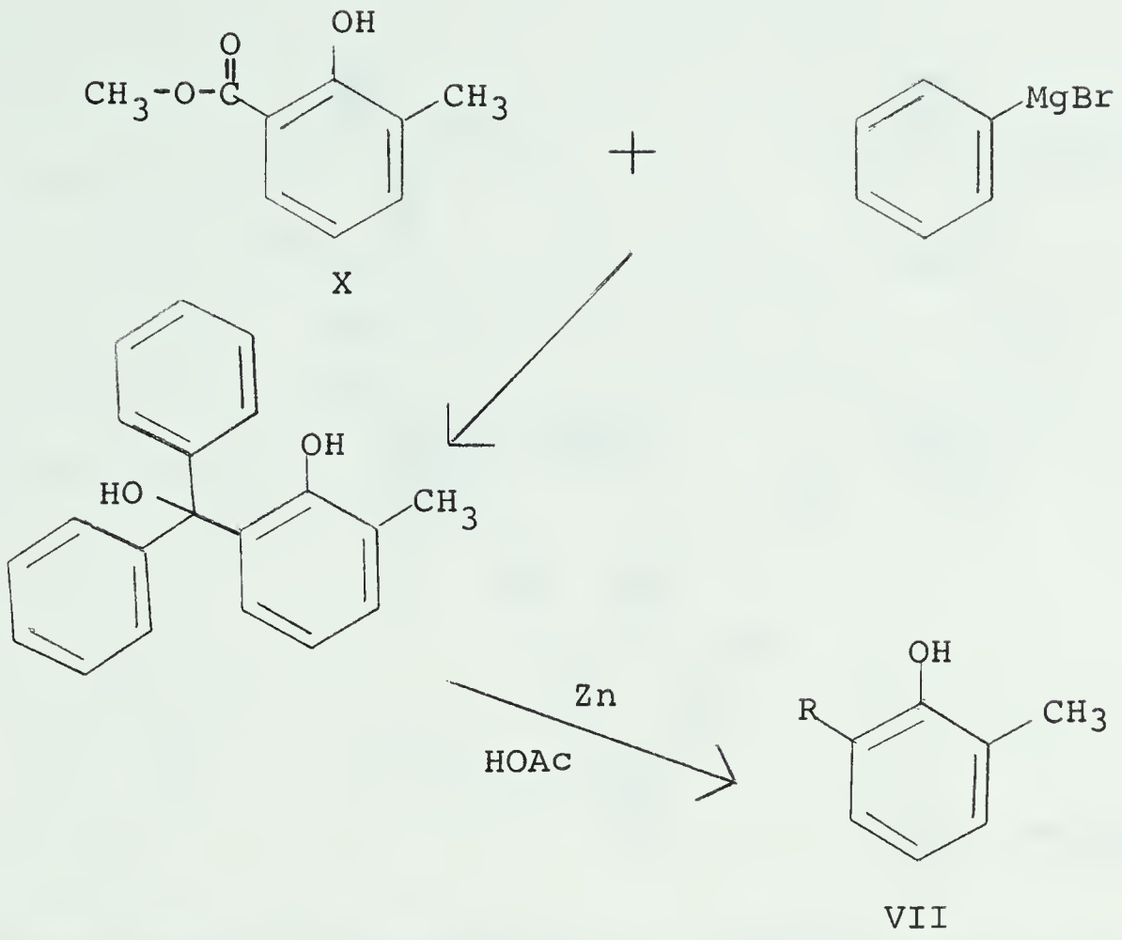
However, when carried out at room temperature, a different product shown to be the para isomer, VIII, was isolated. Assignment of this structure was possible since on bromination of VIII, a product identical to that obtained from the benzhydrylation of 6-bromo-o-cresol (IX) was recovered (equation 1).



(1)

(R = benzhydryl)

In an attempt to verify the structure assigned to product VII, these workers synthesized the compound by an alternate, unequivocal route. Methyl-o-cresotinate (X) was condensed with phenylmagnesium bromide, and the resulting alcohol reduced to the required product with zinc and glacial acetic acid (equation 2).



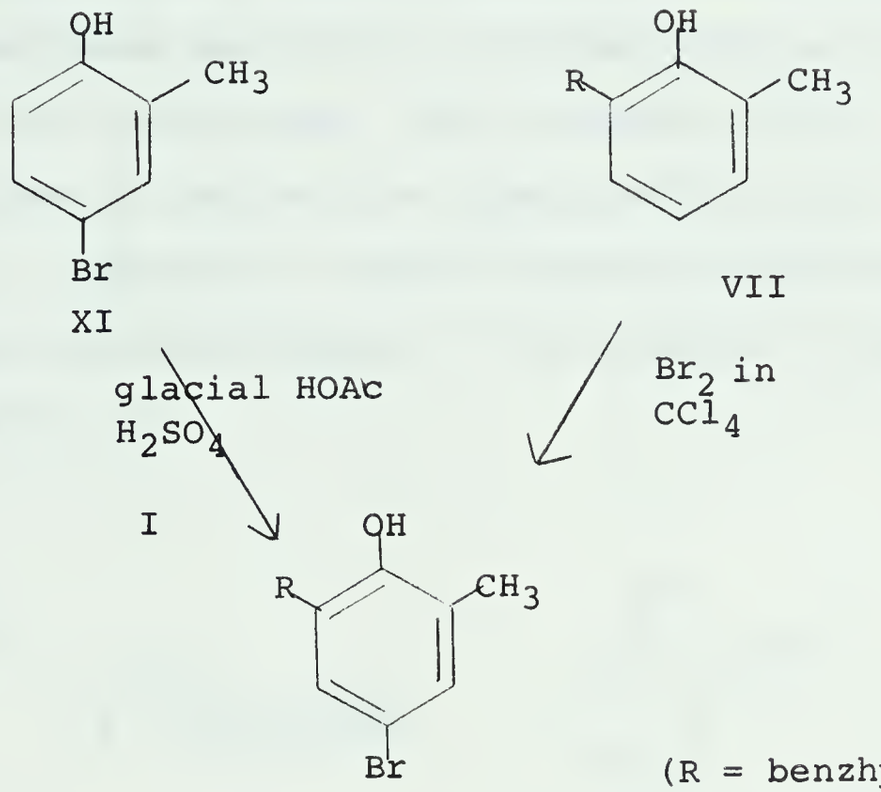
(2)

VII

(R = benzhydryl)

The correctness of this structure once again was established from the fact that the product isolated from the bromination of this compound, (VII), was identical with that recovered from the reaction of 4-bromo-o-cresol (XI) with benzhydrol (equation 3).

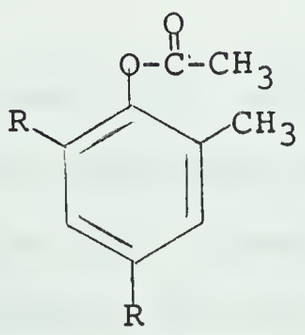
This compound proved to have a different melting point, and to be different from the product previously isolated by both Shorigin (24) and by Iddles and coworkers (26), and purported to be structure VII by Shorigin. Treatment of this latter compound or of compound VIII with benzhydrol in a



(3)

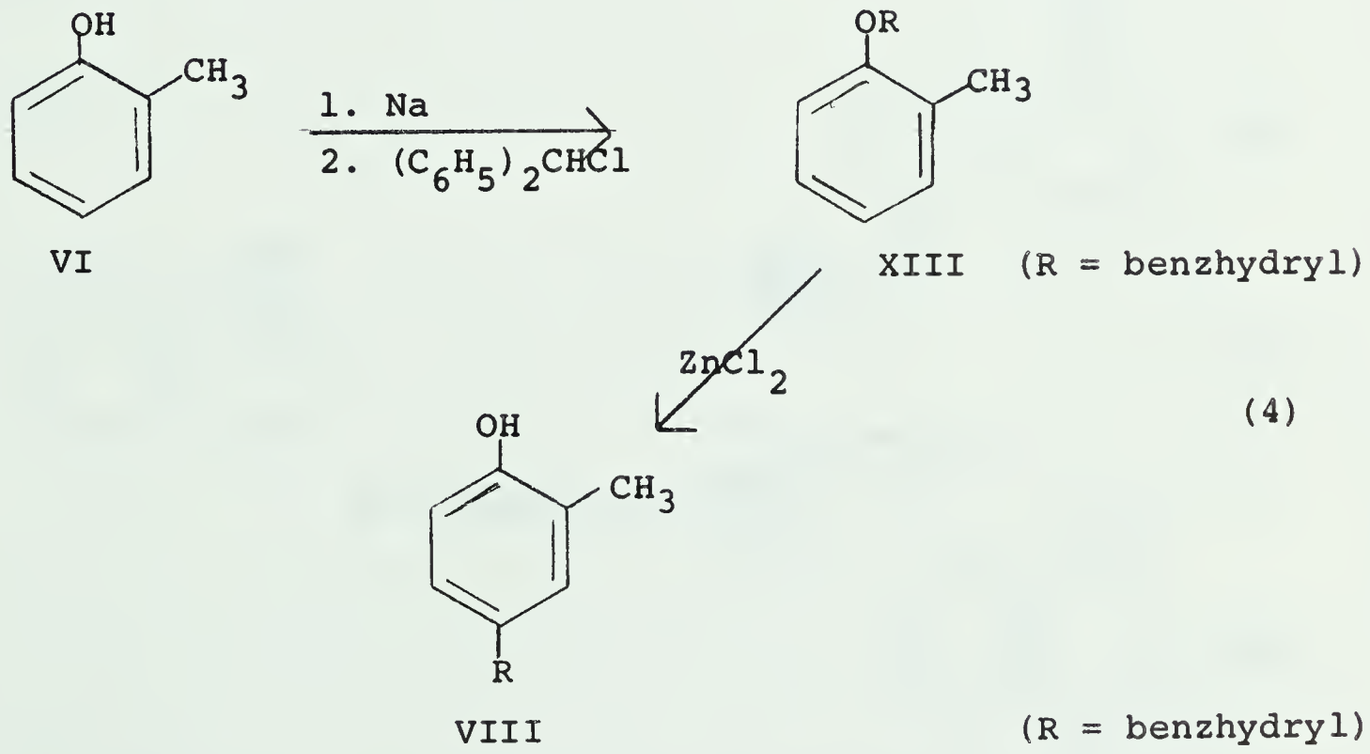
(R = benzhydryl)

sulfuric-acetic acid medium gave a product having a melting point identical with that of the derivative isolated by Shorigin, and to which he had assigned structure VII. This compound was subsequently shown to be 2-methyl-4,6-di(diphenyl-methyl)phenylacetate (XII).



XII (R = benzhydryl)

In a subsequent publication, Iddles et al. (27) reported obtaining compound VIII by the diazotization and hydrolysis of the monosubstituted derivative recovered from the reaction of benzhydrol with o-toluidine. This compound, (VIII), has also been obtained by heating the diphenylmethyl ether of o-cresol (XIII), prepared by treating sodium-o-cresylate in ether with diphenylchloromethane, in the presence of zinc chloride (equation 4).

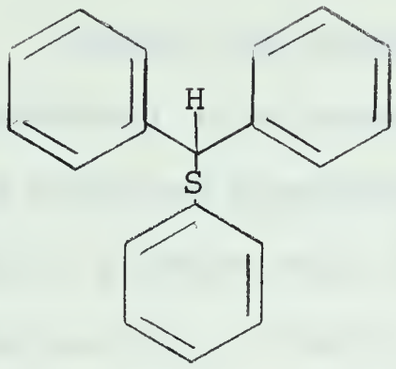


VI XIII (R = benzhydryl)

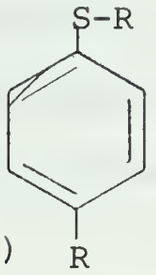
(4)

VIII (R = benzhydryl)

Thiophenols, on the other hand, when reacted with benzhydrol were found to produce thioethers which in turn gave nuclear substituted products (28). Reacting thiophenol with an equimolar ratio of benzhydrol gave the thioether XIV. Employing a two-to-one molar ratio of benzhydrol to the thiophenol, compound XV was recovered.



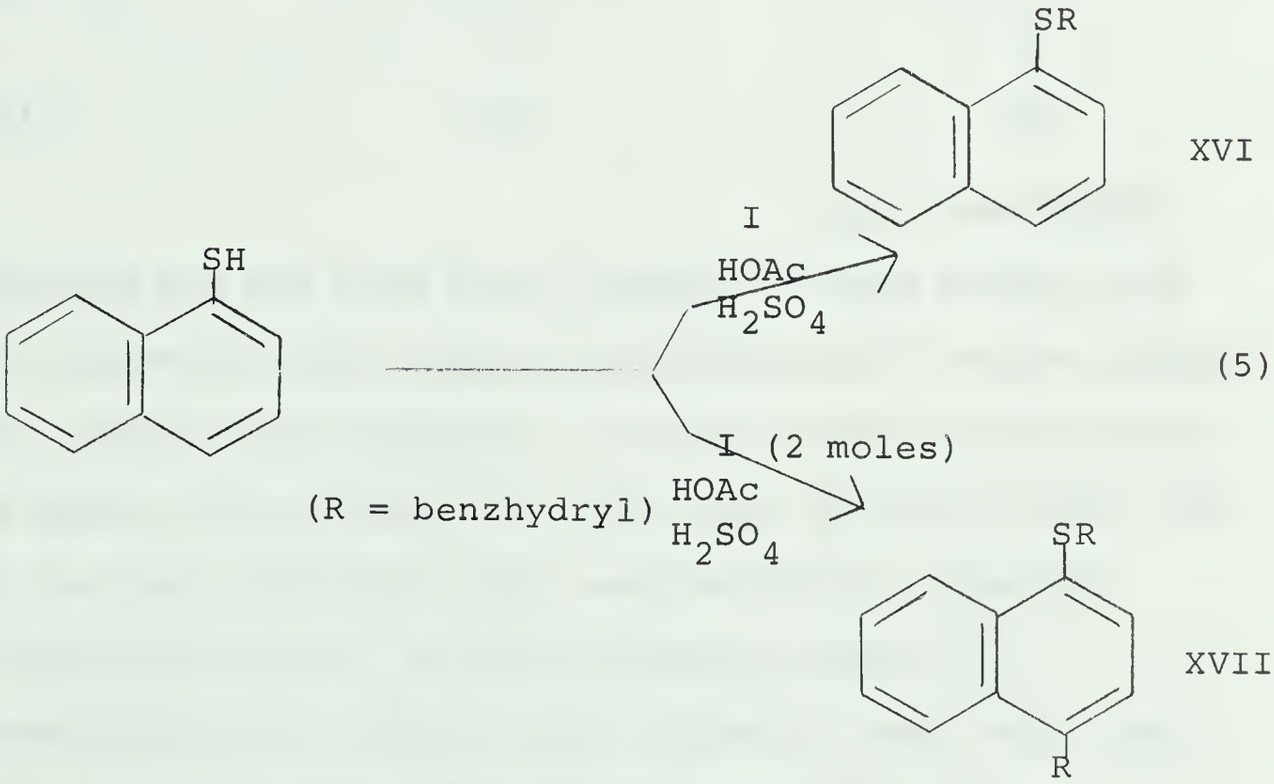
XIV



XV

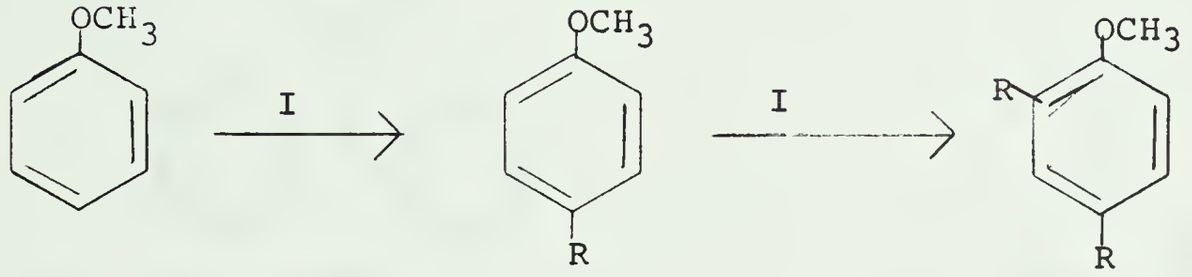
(R = benzhydryl)

Similarly, α-thionaphthol yielded the thioether XVI and the disubstituted product XVII, when one and two moles of benzhydrol respectively, were employed (equation 5).



β-Thionaphthol, when condensed with benzhydrol, afforded only the monosubstituted thioether regardless of the molar ratios of the reactants. Arylethers behave similarly to the phenols and thioethers yielding nuclear substituted products.

Burton and Cheeseman (25) treated anisole (XVIII) with benzhydrol in nitromethane, using perchloric acid as a catalyst, and obtained p-methoxytriphenylmethane (XIX). Reaction of XIX with a further mole of benzhydrol produced 2,4-bisdiphenylmethyl anisole (XX). The 2,4,6-trisubstituted derivative, however, could not be isolated.



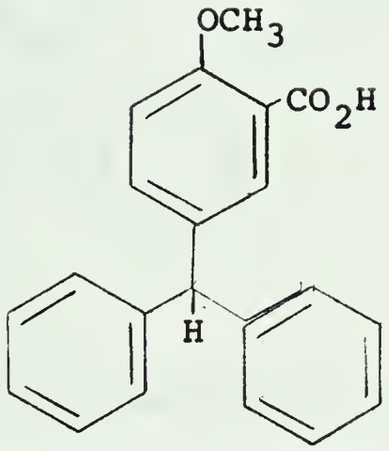
XVIII XIX XX

(R = benzhydryl)

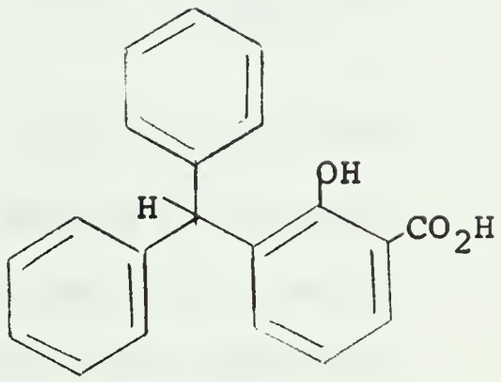
Compound XIX has also been isolated in high yields from a similar reaction using toluene-p-sulfonic acid as the catalyst (21, 29), and as well employing a sulfuric-acetic acid medium (18). Finally, this product has also been obtained using zinc chloride as the condensing agent and benzhydryl chloride, rather than the alcohol, as the alkylating agent (30).

o-Methoxybenzoic acid has been shown to react with benzhydrol to yield the para substituted isomer, XXI (31).

On the other hand, replacement of the methoxy group with a hydroxy group gave the monoalkylated product XXII, substituted in the ortho rather than the para position.



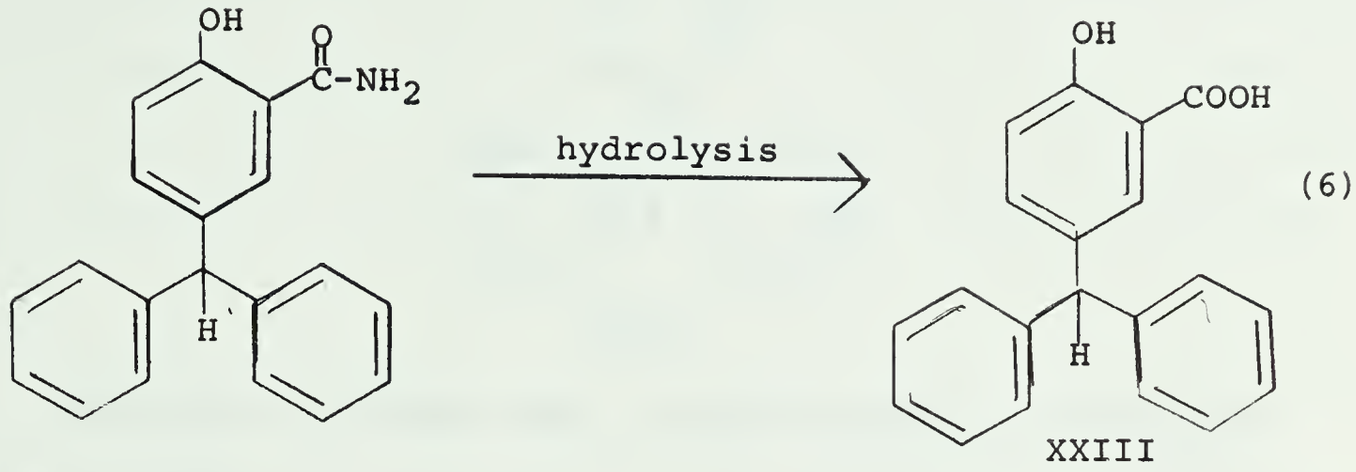
XXI



XXII

Even after careful chromatography of the reaction mixture, none of the para substituted isomer could be detected. This compound, XXIII, has none the less been prepared by the hydrolysis of the amide resulting from the condensation of benzhydrol with salicylamide (31) (equation 6).

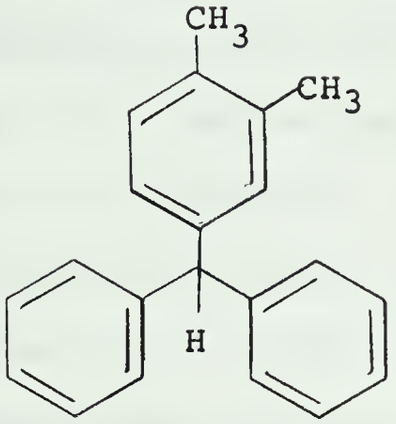
Using a modification of Shorigin's method, Kundiger and Ovist (32) succeeded in alkylating methylbenzenes but failed with benzene and phenanthrene. Using an excess of the hydrocarbon, only monosubstituted products were isolated; where both



XXIII (6)

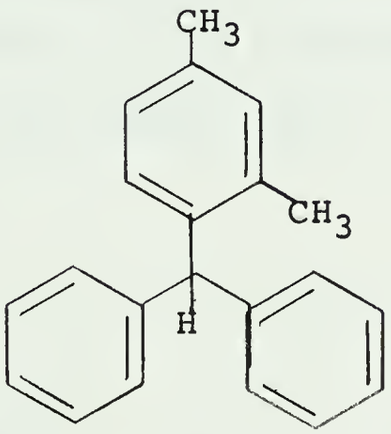
ortho and para substitution was possible, only the para substituted product was isolated. When the para position was blocked, alkylation occurred in the ortho position in about the same yield. Toluene was found to produce the para substituted derivative. This product has also been obtained by carrying out the reaction with toluene-p-sulfonic acid instead of sulfuric acid as the catalyst (21, 29). Dimethylanthracene was isolated from the reaction of toluene, benzhydrol and aluminum chloride. As an explanation of these reactions the authors suggested that benzhydrol could act as a carbon monoxide donor when large amounts of aluminum chloride were used. The hydrocarbon solvent provided the outside rings of the anthracenes, while the carbon monoxide from the carbinol furnished the meso carbons.

o-Xylene reacts with benzhydrol to yield 1-diphenylmethyl-3,4-dimethylbenzene (XXIV).



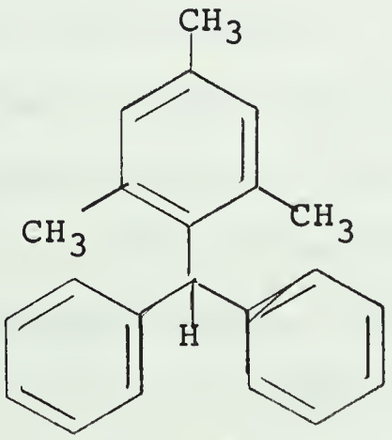
XXIV

Similarly, m-xylene gave 1-diphenylmethyl-2,4-dimethyl-benzene (XXV).



XXV

Mesitylene also was found to condense with benzhydrol to yield diphenylmethylmesitylene (XXVI).

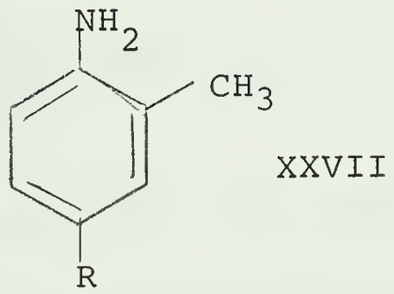


XXVI

The preparation of XXVI has also been reported using toluene-p-sulfonic acid (22) and sulfuric acid (18) as catalysts.

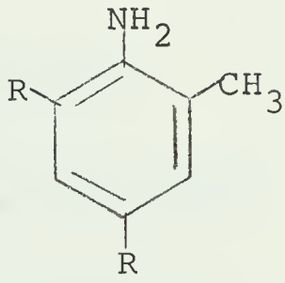
Ungnade and Crandall (33) reacted benzene with benzhydrol, using aluminum chloride as the catalyst. By varying the temperature of the reaction, differing amounts of the following products were obtained: triphenylmethane, triphenylcarbinol, anthracene and tar. Using low temperatures and small amounts of the catalyst only triphenylmethane was produced. By a similar procedure, Huston and Friedman also obtained this latter product (22).

The reaction of o-toluidine with benzhydrol in acetic acid medium led to the isolation of two benzhydryl derivatives, namely compounds XXVII and XXVIII (28).



XXVII

(R = benzhydryl)



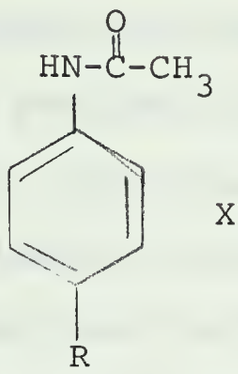
XXVIII

N-diphenylmethyl-o-toluidine which was prepared by other methods, was found to rearrange to XXVII and XXVIII on heating in a hydrochloric-acetic acid medium.

Acetanilide was shown to react with benzhydrol to yield the para substituted product XXIX (19, 34).

Bethell and Gold (18) studied the kinetics of acid catalysed arylalkylations by diphenylmethanols. The formation of a triarylmethane was found to be first order with respect to both (stoichiometric) diphenylmethanol and the aromatic compound.

$$v = k_2 \ [ROH]_{stoich.} \ [ArH]$$ ROH = benzhydrol



XXIX (R = benzhydryl)

The active form of the alkylating agent ROH was found to form in a rapid pre-equilibrium, the equilibrium concentration being low relative to that of the unionized form of the alkylating agent in solution.

$$\left.\begin{matrix} ROH \\ HOAc \end{matrix}\right\} + H^+ \rightleftharpoons R^+ + \left.\begin{matrix} H_2O \\ HOAc \end{matrix}\right\} \quad \text{rapid pre-equilibrium}$$

$$R^+ + ArH \longrightarrow ArR + H^+ \quad \text{rate controlling step}$$

That the latter step was in fact the rate determining step in the reaction was shown by replacing the hydrogen atom in the para position of anisole by deuterium; the rate of alkylation of the para position was found to be the same as with the undeuterated anisole. Therefore the loss of the proton in the intermediate $RArH^+$ was kinetically insignificant. They concluded that diphenylmethylation of anisole was analogous to aromatic nitration, both in the mode of generation of the reactive entity in a rapid pre-equilibrium step, and in the

nature of the substitution step.

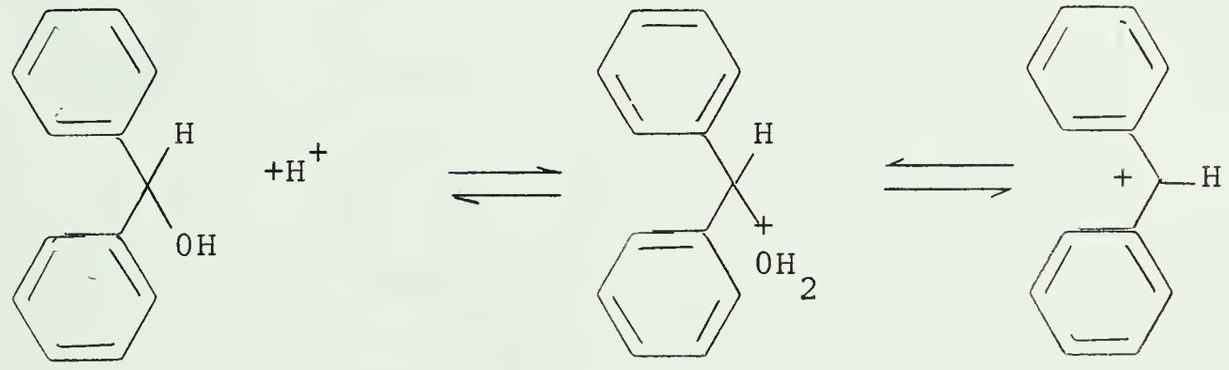
Pratt and Segrave (29) studied the alkylation of aromatic compounds by several para substituted phenylcarbinols. They found that the yields of the products decreased as the electron releasing ability of the para substituent in the carbinol increased, while the yields tended to increase as the electron releasing ability of the substituent on the compound being alkylated increased. It was found that the more reactive phenylcarbinols were more selective in alkylating either of two aromatic compounds; the less stable ions tending to react with the first molecule they encountered, while the more stable ions tended to survive numerous collisions and selected the reaction with the lowest energy requirements. Burton and Cheeseman (25) found that the reactivity towards benzene was in the following order: benzyl > diphenylmethyl > triphenylmethyl cation; this is the reverse of the accepted view of their ease of formation.

Benzhydrol has been condensed with a number of alcohols to yield the corresponding ethers. Pratt and Draper (35) reported obtaining the benzhydryl ethers of butyl and benzyl alcohols using toluene-p-sulfonic acid as the catalyst. Somewhat later Pratt and Segrave (29) observed that the benzhydryl ether of butyl alcohol could not be isolated if an excess of the catalyst was employed. They attributed this to the protonation and inactivation of the oxygen in the butyl alcohol.

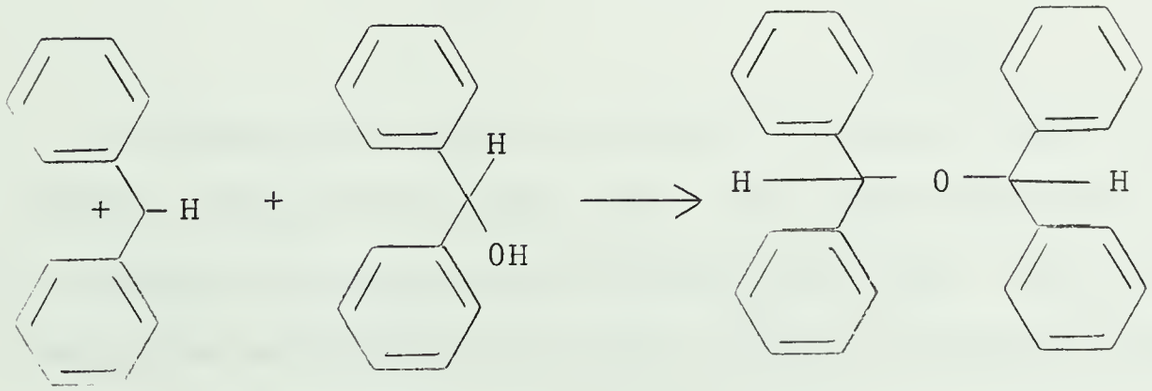
In view of the fact that ether formation has been reported with a number of alcohols, it is not surprising that self-

etherification occurs in reactions of benzhydrol. Thus, bisdiphenylmethyl ether has been recovered as one of the products in the reaction of benzhydrol with a number of amides (36, 37).

Burton and Cheeseman (38) were able to prepare the ether in high yields employing perchloric acid in nitromethane, or in acetic acid. Other workers have employed toluene-p-sulfonic acid as the catalyst (21, 31, 35). The preparation of the ether has also been reported using concentrated sulfuric acid (23). These authors also were successful in preparing the benzhydryl ether of methanol employing this reaction system, although other attempts with conventional

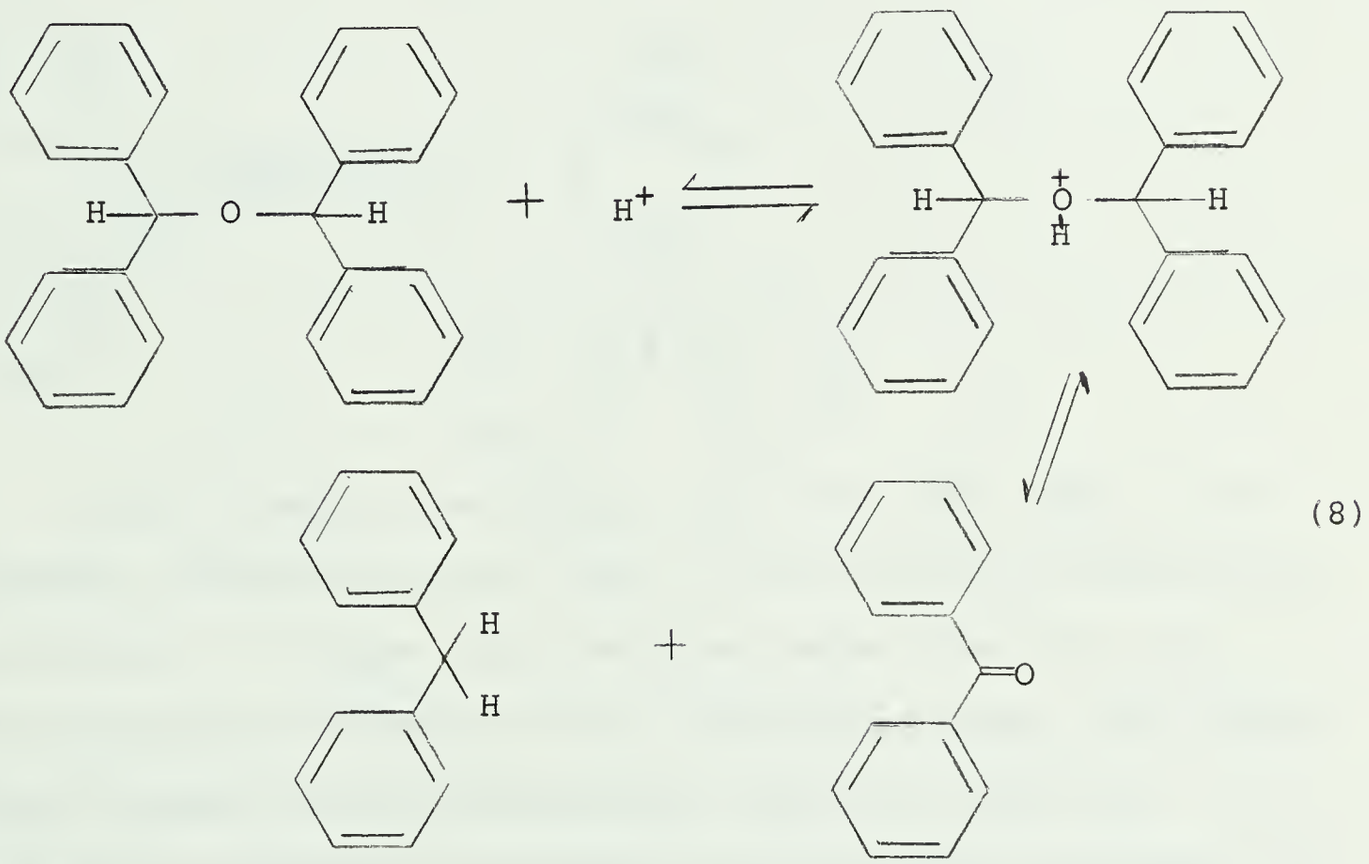


(7)



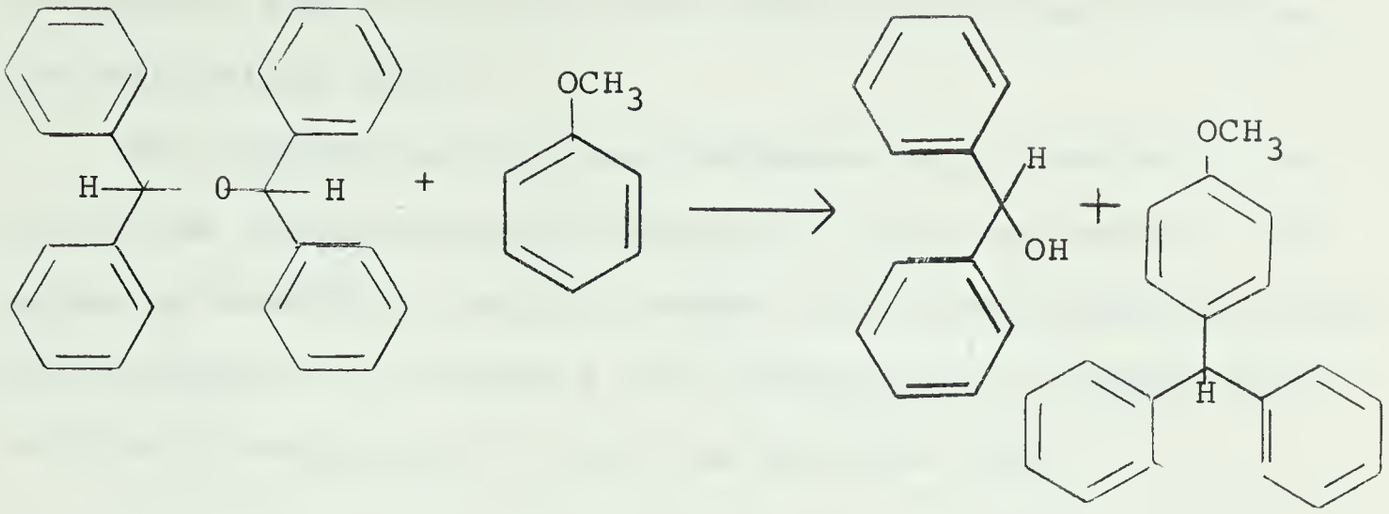
systems failed (39). Burton and Cheeseman (38) proposed the mechanism for the self-etherification of benzhydrol to be that shown by equation 7.

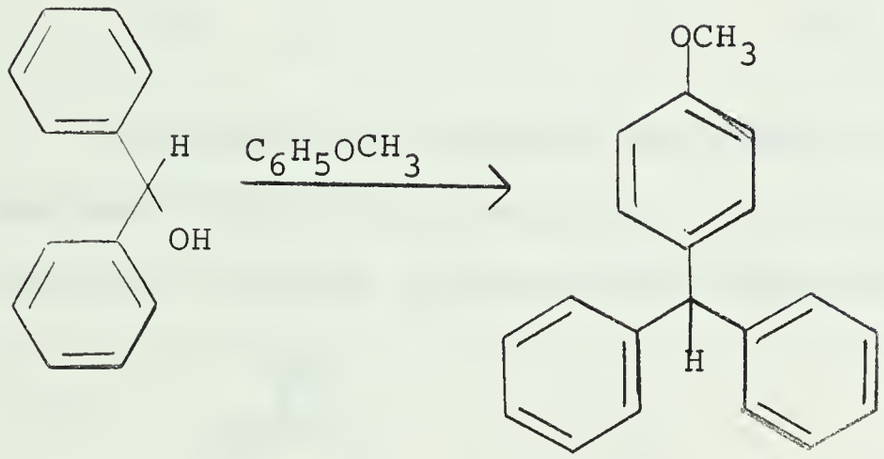
The regeneration of the proton ensures that the reaction is self-perpetuating. Kinetic studies of this reaction revealed that it was first order (40, 41). The ether was found to undergo dismutation on further treatment with acid, presumably via the mechanism shown in equation 8.



(8)

Although benzhydrol is much more basic than the corresponding symmetrical ether (41), the ether has been shown to be capable of acting as an alkylating agent. For example, the alkylation of anisole has been reported using bisdiphenylmethyl ether. The mechanism for the alkylation was postulated to be that illustrated by equation 9.





(9)

Pratt, Preston, and Draper (21) found that when a low catalyst concentration was used in the reaction of benzhydrol in benzene or toluene, the reaction ceased when only half the theoretical volume of water had been evolved. The product they isolated was the dibenzhydryl ether in high yield. If, instead of isolating the product more catalyst was added, or if a higher concentration of the catalyst was used at the start of the reaction, alkylated products of the starting hydrocarbons were isolated. By examination of rate curves in the alkylation of toluene and benzene, it was revealed that most of the

benzhydrol was converted to the ether which then served as the alkylating agent.

Two mercaptans have been condensed with benzhydrol to yield the corresponding thioethers. Pratt and Segrave (29) prepared benzhydryl octylthioether (XXX) from octyl mercaptan; and Holmberg (42) reported the condensation of thioglycolic acid with benzhydrol to give the thioether XXXI.

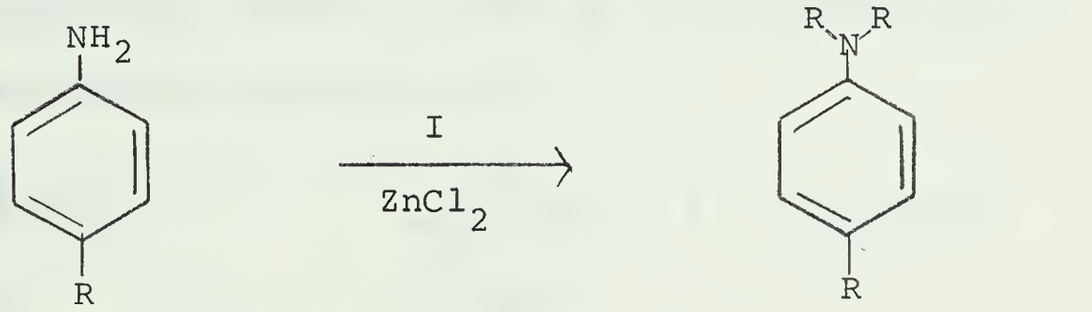
$CH_3(CH_2)_6CH_2$-S-R R = (benzhydryl)

XXX

R-SCH_2COOH

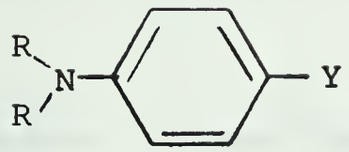
XXXI

Cantarel (43) reported the fusion of p-aminotriphenylmethane (XXXII) with benzhydrol (I), in the presence of zinc chloride, to give p-(dibenzhydrylamino)triphenylmethane (XXXIII).



XXXII (R = benzhydryl) XXXIII

Giraud (44) studied in more detail the reactions of para substituted anilines by Cantarel's method. He found that para substituted anilines reacted almost quantitatively with two moles of benzhydrol to yield N,N-dibenzhydryl derivatives (XXXIV). Not being able to isolate the monobenzhydryl derivatives, Giraud postulated that the dibenzhydryl derivatives were more stable than the N-monobenzhydryl derivatives.



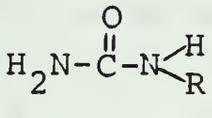
XXXIV

(R = benzhydryl)

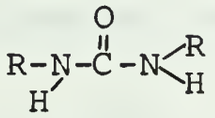
Y = CH_3, $CH(CH_3)_2$, Cl, Br

N-diphenylmethyl derivatives of a variety of amines have been isolated using diphenylmethyl nitrate as the alkylating agent (45). These include aniline, benzylamine, ammonia, morpholine, piperidine and pyridine. Two hydrazines, hydrazine itself, and phenylhydrazine, yielded the respective N-alkylated products.

Urea has been shown to react with benzhydrol to yield the monosubstituted (XXXV) as well as the disubstituted (XXXVI) benzhydryl derivatives (19).



XXXV



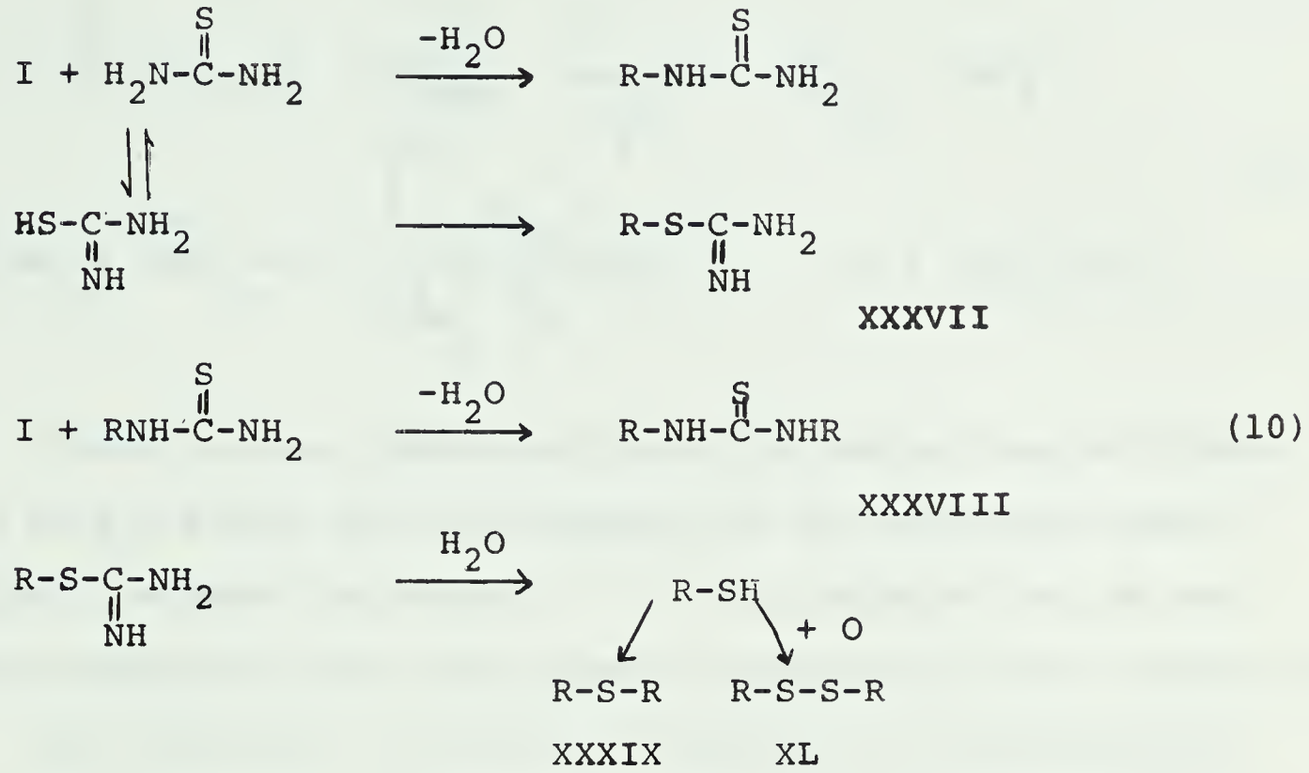
XXXVI

R = benzhydryl

The latter product has also been obtained employing diphenylmethyl nitrate as the alkylating agent (45).

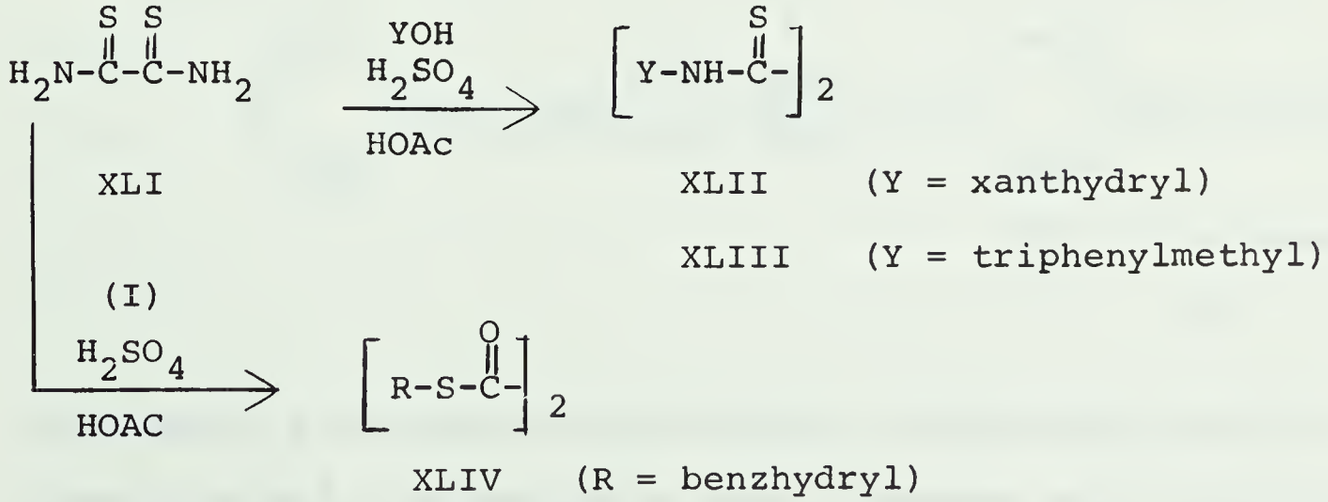
In addition to treating urea with benzhydrol, to also obtain XXXVI, Rahman and Singh (36) found that thiourea produced a variety of products including: S-(diphenylmethyl) isothiourea (XXXVII), N, N'-bis (diphenylmethyl) thiourea (XXXVIII), bis (diphenylmethyl) sulphide (XXXIX) and bis (diphenylmethyl) disulphide (XL). They postulated a mechanism

shown by equation 10 to explain the products they isolated.

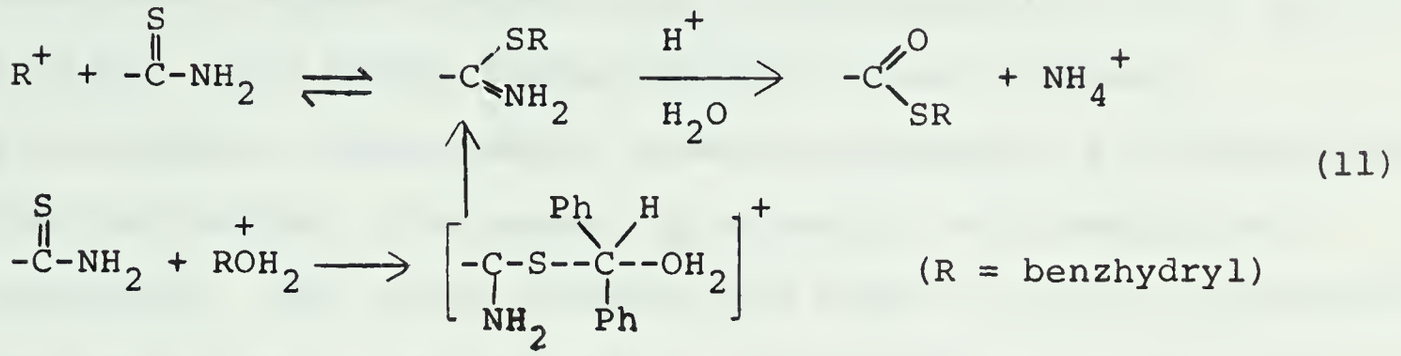


(10)

Although dithioxamide (XLI) yielded the expected product when reacted with xanthydrol (XLII), and with triphenylcarbinol (XLIII), with benzhydrol the product isolated was dibenzhydryl dithioloxalate (XLIV).



Two different mechanisms were proposed to explain this result. These are shown in equation 11.

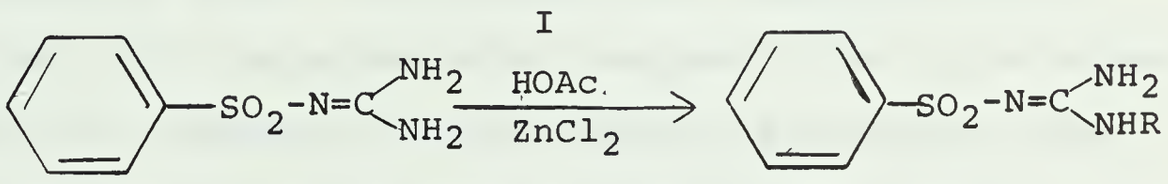


(11)

(R = benzhydryl)

These workers postulated that the product may be formed via an S_N2 attack by dithiooxamide on the protonated benzhydrol, as shown by equation 11. This hydrated cation was also considered to be the reactive species by other workers (25).

By refluxing a solution of benzhydrol, phenylsulfonylguanidine and zinc chloride in acetic acid, Sukhoruchkin and Burmistrov (46) were able to isolate 2-phenylsulfonyl-1-benzhydrylguanidine (XLV) (equation 12).



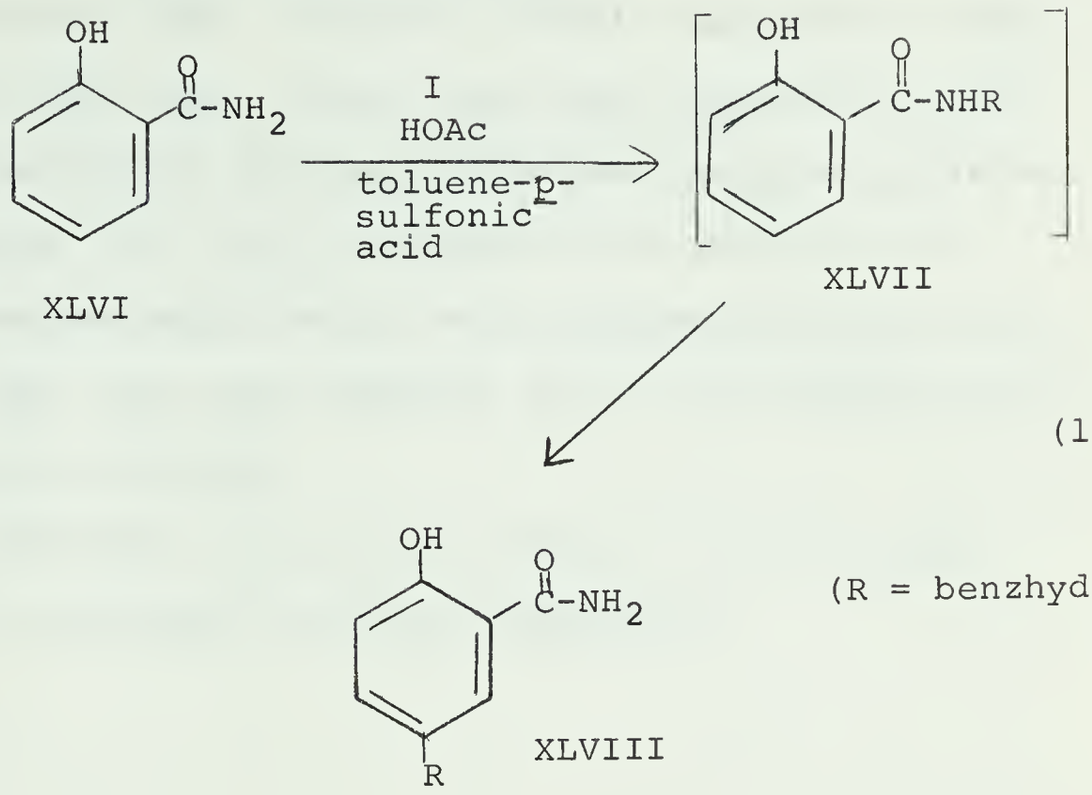
XLV (R = benzhydryl)

(12)

Similarly, p-tosylsulfonylguanidine, p-chlorophenylsulfonylguanidine and nitroguanidine, when condensed with benzhydrol yielded the corresponding monosubstituted derivatives.

A variety of primary amides have been shown to react with benzhydrol. Cheeseman and Poller (19) isolated derivatives of twenty-one selected amides using toluene-p-sulfonic acid as the catalyst. The amides reacted by this method included: n-butyramide, isobutyramide, p-methoxybenzamide, p-nitrobenzamide, phenylacetamide, o-toluamide, p-toluamide, succinamide and malonamide. The latter compound was shown to yield a disubstituted derivative. The derivatives of acetamide and benzamide were also prepared, these having been reported previously starting with the nitrate, rather than the alcohol (45). Propionamide (19, 47), chloroacetamide (19, 48, 49), formamide (19, 37, 45) and o-methoxybenzamide (31), have also been treated with benzhydrol to give the corresponding monosubstituted derivatives. The resulting compounds were assumed to be the corresponding N-diphenylmethyl derivatives, but no attempts were made at verifying these structures.

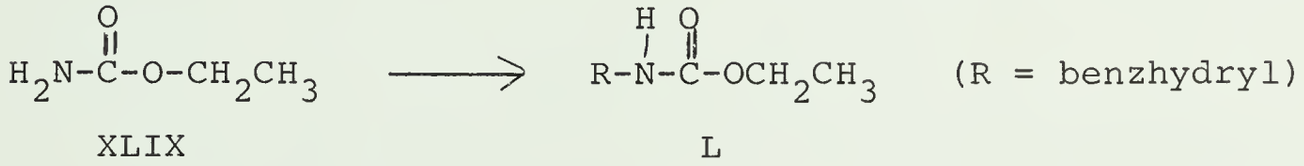
Salicylamide (XLVI), on reaction with benzhydrol, was found to yield the ring substituted compound shown by structure XLVIII (19, 31). However, N-diphenylmethyl alicylamide (XLVII), which was prepared by an indirect synthesis, was found to rearrange to XLVIII in an acetic-toluene-p-sulfonic acid medium. It was therefore concluded that any N-diphenylmethyl derivatives formed during the reaction of benzhydrol with salicylamide would rearrange to compound XLVIII as shown by equation 13.



(13)

(R = benzhydryl)

Urethane (XLIX) has been shown to yield the corresponding N-diphenylmethyl derivative (L) on reaction with either benzhydrol (19) or benzhydryl nitrate (45).



Although the corresponding N-diphenylmethyl derivatives of benzenesulfonamide, toluene-p-sulfonamide (19, 40, 45) and methanesulfonamide (45) have been reported, there are no reports in the literature of condensations involving sulfanilamides.

Although benzhydrol normally reacts via its carbonium ion, the reaction may also proceed by an attack of the pair of electrons of the benzhydrol oxygen and subsequent loss of the

alcoholic hydrogen atom. However, as with xanthydrol, these reactions are very rare. Esters have been reported by the reaction of benzhydrol with acid chlorides, such as p-nitrobenzoyl chloride (50) and p-toluenesulfonyl chloride (51). Benzhydrylmethylmercaptoacetate and benzhydrylmethylmercaptopropionate have also been prepared (52), also employing the appropriate acid chloride.

To our knowledge, this is the extent of the recorded information on reactions involving benzhydrol.

RESULTS AND DISCUSSION

The apparent success of an acetic-sulfuric acid medium in previously reported alkylations involving benzhydrol prompted attempts on similar lines.

Refluxing solutions of sulfanilamides with benzhydrol in the above medium for periods of one half hour, and addition to water provided gums which could not be crystallized. However, several sulfanilamides gave solid products, but in very low yields. In an attempt to increase the yield, the concentration of sulfuric acid was increased and the solutions were refluxed for longer periods of time. In some instances the yields were increased, but remained relatively low. The majority of the products obtained by this method exhibited melting points greater than 300°C. Sulfadiazine produced a product in very good yield, but it proved very difficult to recrystallize to a constant melting point.

Since p-toluenesulfonic acid had also been employed as a catalyst by various workers (19, 21, 22, 29, 31, 35) with good success, its suitability was tested with a variety of sulfanilamides.

As with sulfuric acid, this system after refluxing the same length of time produced unresolvable gums. Attempted reactions at room temperature with several sulfanilamides yielded the starting materials. Considering the possibility of amino protonation, thereby inactivating the nucleophilic properties of the aniline portion of the sulfanilamides, the

sulfanilamides, dissolved in dimethylformamide, were dripped into a refluxing solution of benzhydrol and the acid. Sulfanilamide yielded a product which was never characterized, but the other sulfanilamides treated by this method failed to yield derivatives.

In view of the disappointing results obtained with sulfuric and p-toluenesulfonic acids, attention was turned to another acid catalyst, namely perchloric acid. Burton and Cheeseman (25) were able to condense benzhydrol with phenol, in a nitromethane solvent, employing this acid as a catalyst.

Preliminary studies with several sulfonamides using the above solvent system proved reassuring. Refluxing equimolar amounts of the sulfanilamide and alcohol with small amounts of acid in nitromethane for 45 minutes, while stirring electromagnetically, resulted in the precipitation of a solid material on cooling. The crude products were obtained in good yields, were easily purified, and were devoid of the instability that confronted Moskalyk and Chatten (1) with xanthydrol derivatives.

By varying reaction times with several sulfanilamides, it was found that a 45 minute reflux time produced the best yields. It was also found that the reaction would yield only starting materials if carried out at room temperature. Since the sulfanilamides employed in this study were all closely structurally related, it was expected that they would all react in a similar fashion. Therefore, the condensation of all the sulfanilamides was attempted by this procedure. Although this

procedure was adequate with slight modifications for the majority of the sulfanilamides, a significant number failed to yield any products. Generally, for those sulfanilamides which did not provide derivatives, upon refluxing for 45 minutes, the reaction mixture had turned a dark red-black colour. Cooling the solution failed to yield a precipitate, and evaporating the nitromethane and cooling provided only gums. All attempts at isolating crystalline materials were unsuccessful.

Considering the possibility of instability of the sulfanilamide derivatives under these conditions, two modifications in the procedure were undertaken. Firstly, a change in the reaction conditions to a milder nature by using a lower temperature, for shorter periods of time, was studied. The other modification was replacing perchloric acid by the milder acid, hydrochloric acid. The reaction was carried out under reflux for the standard 45 minutes. Both modifications proved useful, and by using these procedures derivatives of all the sulfanilamides attempted, with the exception of sulfisomidine, were isolated. It was found that some sulfanilamides produced derivatives by each of the procedures mentioned.

The C, H, and N analyses of the benzhydryl derivatives are shown in Table I. The products isolated were either the mono, di or tribenzhydryl derivatives. It can be seen from the Table that for each of the dibenzhydryl sulfanilamide derivatives isolated, the monobenzhydryl derivative of that

TABLE I

Mono, Di- and Tribenzhydryl-N^1-Monosubstituted Sulfanilamides

Ref. No.**	Sulfanilamide N^1-	Generic Name	Melting Point °C	Recrystallizing solvent	Formula	Analysis Calculated C	Calculated H	Calculated N	Found C	Found H	Found N
1	-	Sulfanilamide	175-176	Acetone-water	$C_{19}H_{18}N_2O_2S$	67.20	5.36	8.25	67.05	5.10	8.50
1t	-	Sulfanilamide	206-208	Ethanol	$C_{45}H_{38}N_2O_2S$	80.56	5.71	4.18	80.51	5.89	4.15
2	2-Pyrimidyl	Sulfadiazine	253-255	Acetone water	$C_{23}H_{20}N_4O_2S$	66.32	4.84	13.45	66.36	4.93	13.81
3	2-Pyridyl	Sulfapyridine	212-214	Acetone-water	$C_{24}H_{21}N_3O_2S$	69.37	5.10	10.11	69.19	4.81	10.39
4	4-Methyl-2-pyrimidyl	Sulfamerazine	213.5-215	Acetone-water	$C_{24}H_{22}N_4O_2S$	66.95	5.15	13.02	66.94	5.11	13.25
5	4,6-Dimethyl-2-pyrimidyl	Sulfamethazine	200.5-202	Ethanol-water	$C_{25}H_{24}N_4O_2S$	67.54	5.44	12.61	67.36	5.45	12.45
6	5-Methyl-1,3,4-thiadiazol-2-yl	Sulfamethizole	212-212.5	Acetone-water	$C_{22}H_{20}N_4O_2S_2$	60.52	4.62	12.84	60.37	4.65	12.52
6d	"	"	224-225	Acetone-water	$C_{35}H_{30}N_4O_2S_2$	69.74	5.02	9.29	69.77	4.82	9.22
7	6-Chloro-3-pyridazinyl	Sulfachloropyridazine	226.5	Ethanol-water	$C_{23}H_{18}ClN_4O_2S$	61.40	4.03	12.45	61.72	4.03	12.65
8	6-Methoxy-3-pyridazinyl	Sulfamethoxypyridazine	206-208	Acetone-water	$C_{24}H_{22}N_4O_3S$	64.55	4.97	12.55	64.85	5.35*	12.51
9	Acetyl	Sulfacetamide	208-208.5	Acetone-water	$C_{21}H_{20}N_2O_3S$	66.29	5.30	7.36	66.25	5.46	7.29
10	Guanyl	Sulfaguanidine	244-246	Acetone-water	$C_{20}H_{20}N_4O_2S$	63.13	5.30	14.73	63.13	5.64	14.42

continued

TABLE I (continued)

11	1-Phenyl-5-pyrazolyl	Sulfaphenazole	238-239	Acetone-water	$C_{28}H_{24}N_4O_2S$	69.98	5.03	11.66	70.04	4.73	11.50
12	2-Quinoxalinyl	Sulfaquinoxaline	224-225	Acetone-water	$C_{27}H_{22}N_4O_2S$	69.51	4.75	12.01	69.63	4.90	12.25
13	Phenyl	Sulfanilanilide	153-154	Acetone-water	$C_{25}H_{22}N_2O_2S$	72.43	5.35	6.76	72.81	5.61	6.97
13d	Phenyl	Sulfanilanilide	236-238	Ethanol	$C_{38}H_{32}N_2O_2S$	78.59	5.56	4.82	78.51	5.59	4.60
13d'	Phenyl	Sulfanilanilide	216-218	Acetone-water	$C_{38}H_{32}N_2O_2S$	78.59	5.56	4.82	78.08*	5.88	4.82
14	5-Methyl-3-isoxazolyl	Sulfamethoxazole	209-209.5	Acetone-water	$C_{23}H_{21}N_3O_3S$	65.85	5.05	10.02	65.67	4.98	9.95
15	2,6-Dimethoxy-4-pyrimidyl	Sulfadimethoxine	175-176	Ethanol-water	$C_{25}H_{24}N_4O_4S$	63.01	5.07	11.76	62.85	5.17	11.73
15t	"	"	178-179	Acetone-water	$C_{51}H_{44}N_4O_4S$	75.77	5.38	6.92	75.64	5.08	6.69
16	p-Isopropoxybenzoyl	Sulfaproxyline	200.5-201.5	Ethanol-water	$C_{29}H_{28}N_2O_4S$	69.58	5.64	5.60	69.78	5.52	5.86
17	3,4-Dimethyl-5-isoxazolyl	Sulfisoxazole	188-188.5	Ethanol-water	$C_{24}H_{23}N_3O_3S$	79.18	5.65	4.62	79.23	5.46	4.85
17d	"	"	207-208	Ethanol	$C_{37}H_{33}N_3O_3S$	74.10	5.55	7.01	73.95	5.46	7.30
18	2-Thiazolyl	Sulfathiazole	229.5-230.5	Ethanol-water	$C_{22}H_{19}N_3O_2S_2$	62.68	4.54	9.97	62.59	4.63	10.27
19	5-Ethyl-1,3,4-thiadiazol-2-yl	Sulfaethylthiadiazole	197	Acetone-water	$C_{23}H_{22}N_4O_2S_2$	61.17	5.13	12.41	61.23	4.91	12.20
19d	"	"	207.5-208.5	Acetone-water	$C_{36}H_{33}N_4O_2S_2$	69.99	5.38	9.07	70.77*	5.54	8.16

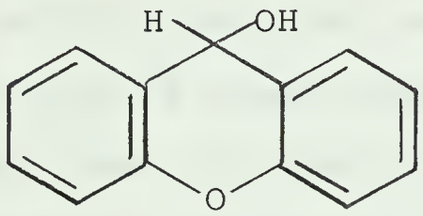
** - d refers to a disubstituted and t to a trisubstituted derivative
* - these compounds could not be purified further

sulfanilamide was also obtained. The differences in the degree of substitution resulted from varying the molar ratios of benzhydrol to the sulfanilamide used in the reaction.

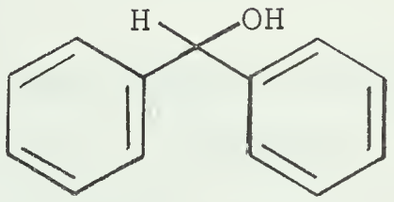
Structural Determination

Monobenzhydryl -N^1-Monosubstituted Sulfanilamides

Considering the structural similarity of xanthydrol (LI), and benzhydrol (I), it was expected that these alcohols would react in a similar fashion with sulfanilamides.



LI



I

Although Moskalyk and Chatten (1) had no reference to previous condensations of similar aromatic alcohols with sulfanilamides, they were able to show that the 9-xanthenyl radical condensed without exception on the N^4-position of the sulfanilamide molecule. The site of substitution of the second 9-xanthenyl moiety in the dixanthenyl derivatives was shown to be one of the following positions:

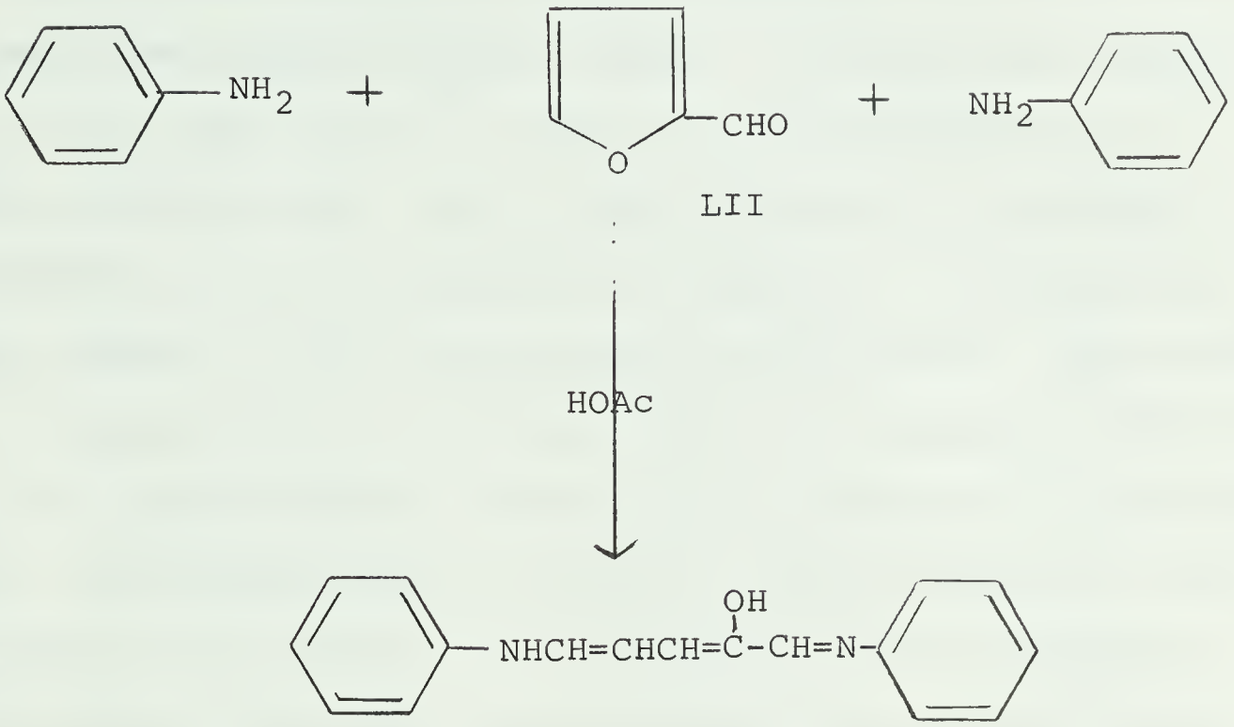
(i) on the annular nitrogen atom of the heterocyclic ring, as a result of condensation with the imino tautomeric form of the sulfanilamide.

(ii) on the extra ring nitrogen atom at the N^1-position, reaction having occurred with the amino tautomeric form.

(iii) on the activated 5-position of the pyrimidine ring.

However, the product from the reaction of benzhydrol with o-toluidine (28) implied that ring substitution was favored over nitrogen substitution when using this alcohol as the alkylating agent. Ring substitution also occurs with phenols (24, 25, 26). Although benzhydrol has been shown to react with a variety of amides, these were limited to primary amides. Since sulfanilamides, with the exception of sulfanilamide itself, are secondary amides, the likelihood of substitution at this position seemed remote.

In view of these facts, a method was sought to distinguish nitrogen from ring substitution, in order to determine where substitution had occurred. Qualitative color tests to detect the presence or absence of the primary aromatic amino function appeared to be a reasonable preliminary approach. Although diazotization and coupling is the most common method of detecting the primary aromatic amino group, it was not deemed suitable as a qualitative test in this study for the following reasons: Moskalyk and Chatten (1) found that secondary amines produced from the reaction of sulfanilamides with xanthydrol gave a positive primary test. This was later found to be the result of cleavage of the xanthenyl group under the conditions of the test. Also, a sizeable amount of sample is required. Furfural (LII), has been successfully employed (1, 53) as a reagent to detect this functional group by the formation of a coloured conjugated Schiff's base as shown by equation 14 (54).



(14)

As opposed to diazotization and coupling, the furfural test is almost instantaneous and requires only a fraction of a milligram of sample. By adding a drop of an acetic acid solution of furfural to the test sample in a spot plate, a change from yellow to bright red constitutes a positive test.

Applying this test to the monosubstituted derivatives listed in Table I, negative results were obtained in each instance. This failure to give a positive furfural test indicated N^4-substitution. To confirm the result of the colour test, the infrared spectra of the monobenzhydryl

derivatives were recorded and compared with those of the parent compounds previously reported (1). The spectra of the parent sulfanilamides exhibit two bands in the 3500-3300 cm^{-1} region characteristic of the stretching vibration of an unsubstituted primary aromatic amine. An additional absorption in the 1640-1590 cm^{-1} region is also displayed by the parent sulfanilamides. This latter absorption is normally attributed to the N-H deformation frequency. On examination of the spectra of the monobenzhydrylsulfanilamide derivatives, only a single band in the former region was observed (Table II). This is a distinguishing feature for the presence of secondary amines. The second region referred to above proved of little diagnostic value because of the presence of C=C stretching absorptions in the region thereby making the interpretation extremely difficult and unreliable. As an additional proof for the site of substitution, all the derivatives were titrated nonaqueously. Inability to titrate would have shown the absence of the amide proton, however, with the exception of sulfanilamide, sulfaguanidine, and sulfanilanilide, all the derivatives proved titratable (Table III). The inability of sulfaguanidine to titrate was not alarming since sulfaguanidine itself cannot be titrated (55) due to its very weak acidic nature (56). Similarly, sulfanilamide itself is not titratable. The failure of the sulfanilanilide derivative to titrate is however unexplainable. Accordingly, the monobenzhydryl derivatives presented in Table I may be assigned the corresponding N^4-monosubstituted structures (LIII).

TABLE II

The N-H Stretching Vibrations of the N^4-Benzhydryl-N^1-Monosubstituted Sulfanilamides

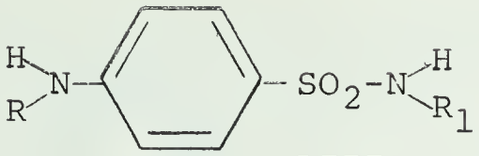
Ref. No.	Derivative of	ν NH (cm^{-1})	
		Parent*	Derivative
1	Sulfanilamide	3430,3305	3330
1t	Sulfanilamide	3430,3305	3425
2	Sulfadiazine	3390,3310	3390
3	Sulfapyridine	3384,3279	3367
4	Sulfamerazine	3442,3333	3390
5	Sulfamethazine	3401,3300	3289
6	Sulfamethizole	3384,3284	3356
6d	Sulfamethizole	3384,3284	3311
7	Sulfachloropyridazine	3472,3362	3367
8	Sulfamethoxypyridazine	3448,3356	3356
9	Sulfacetamide	3478,3372	3378
10	Sulfaquanidine	3367,3305	3436,3378,3311
11	Sulfaphenazole	3390,3300	3367
12	Sulfaquinoxaline	3413,3322	3556
13	Sulfanilanilide	3367,3306	3268
13d	Sulfanilanilide	3367,3306	3484,3361
13d'	Sulfanilanilide	3367,3306	3333
14	Sulfamethoxazole	3390,3289	3356
15	Sulfadimethoxine	3390,3279	3311
15t	Sulfadimethoxine	3390,3279	3356
16	Sulfaproxyline	3431,3350	3333
17	Sulfisoxazole	3436,3322	3390
17d	Sulfisoxazole	3436,3322	3289
18	Sulfathiazole	3279,3226	3300
19	Sulfaethylthiadiazole	3442,3322	3333
19d	Sulfaethylthiadiazole	3442,3322	3279

* Taken from (1)

TABLE III

Nonaqueous Titration of Monobenzhydryl-N^1-Monosubstituted Sulfanilamides

Ref. No.	N^4-Benzhydryl derivative of	Molecular Weight	
		Calculated	Found
1	Sulfanilamide	338.42	-
2	Sulfadiazine	416.49	414.62
3	Sulfapyridine	415.50	416.87
4	Sulfamerazine	430.52	429.23
5	Sulfamethazine	444.54	448.05
6	Sulfamethizole	436.54	442.08
7	Sulfachloropyridazine	449.92	464.20
8	Sulfamethoxypyridazine	446.51	440.51
9	Sulfacetamide	380.46	379.32
10	Sulfaquanidine	380.46	-
11	Sulfaphenazole	480.57	485.86
12	Sulfaquinoxaline	414.52	404.32
13	Sulfanilanilide	414.52	-
14	Sulfamethoxazole	419.49	414.42
15	Sulfadimethoxine	476.54	476.19
16	Sulfaproxyline	500.60	506.80
17	Sulfisoxazole	433.51	440.14
18	Sulfathiazole	421.52	423.12
19	Sulfaethylthiadiazole	450.58	447.21



LIII

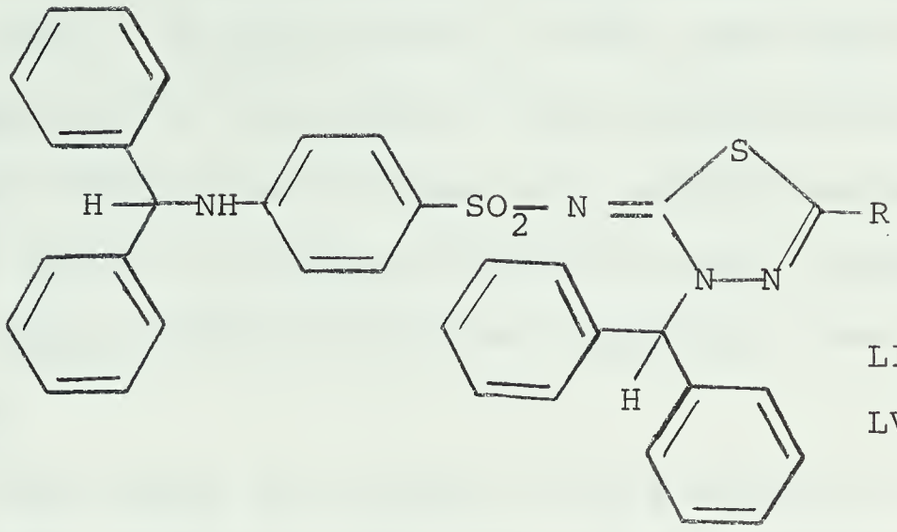
(R = benzhydryl)

(R_1 = appropriate substituent as shown in Table I)

Dibenzhydryl-N^1-Monosubstituted Sulfanilamides

Three of the sulfanilamides which afforded disubstituted derivatives, were previously shown to yield dixanthenyl derivatives with xanthydrol (1). Three different sites of substitution were observed for the second xanthenyl moiety in these derivatives. Since similar sites of substitution would be expected with benzhydrol, proof for each of these was sought, based on evidence similar to that employed by Moskalyk and Chatten (1) for assigning the various structures.

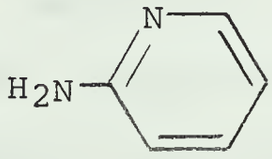
The dibenzhydryl derivatives of sulfamethizole (ref. no. 6d) and the ethyl homolog (ref. no. 19d) were shown to possess structures similar to those found for the corresponding dixanthenyl derivatives (1). Based mainly on the positions of the SO_2 symmetric stretching frequencies of these compounds in the infrared region, Moskalyk and Chatten (1) were able to show that the second alkyl group in these compounds was occupying the annular nitrogen atom of the heterocyclic ring, reaction having occurred from the imido tautomeric form. A similar reaction site would yield the following compounds with sulfamethizole (LIV) and sulfaethylthiadiazole (LV) respectively.



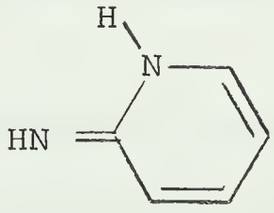
LIV, R = CH_3

LV, R = C_2H_5

Studies on prototropic tautomerism of heteroaromatic compounds have revealed that α- and γ-amino derivatives of N-heteroaromatic compounds exist in the amino form and not as the imino compound. Thus 2-aminopyridine for example, exists as LVI and not LVII (57, 58, 59, 60). This would be only



LVI



LVII

logical since LVI is in the more favorable aromatic form. Sheinker (60) attributed this to the relative basicities of the two nitrogens involved. Thus, substitution of the extra ring nitrogen atom with an electronegative group would reduce the relative basicity of this nitrogen and thereby affect the amine-imine tautomeric equilibrium. Therefore, the sulfanilic

acid radical in N^1-monosubstituted sulfanilamides would be expected to have a variable effect on the amido-imido equilibrium, depending on the nature of the heteroaromatic amine. This has been found to be the case with sulfanilamides. The existence of either of these two forms has been investigated by several physical methods such as ultraviolet and infrared spectroscopy.

It has been found that there is one maximum for the amino form ($-N=\overset{|}{C}-\overset{|}{N}-SO_2$) and two maxima for the imino form ($-\overset{|}{N}-\overset{|}{C}=N-SO_2-$) in the ultraviolet region (61, 62, 63).

In the infrared region, Sheinker et al. (62) reported that these forms could be distinguished by several spectral differences in the 1000-900 cm^{-1} region. They assigned the 940 cm^{-1} band as being characteristic of the imino ($-\overset{|}{N}-\overset{|}{C}=N-SO_2$) grouping, and bands at 1040 cm^{-1} and 860-850 cm^{-1} as being typical of the amino ($-N=\overset{|}{C}-\overset{|}{N}-SO_2-$) structure.

The relative position of the SO_2 symmetric stretching frequency, which normally occurs in the 1170-1130 cm^{-1} region, has been employed as a means of distinguishing these tautomeric forms (1, 64, 65).

Uno et al. (64) found that the above stretching frequency appeared low in the region for sulfonamides having the imido structure when compared with the corresponding amido tautomer. This difference in the SO_2 symmetric stretching frequency between the amido and the imido form may be attributed to the difference in the SO double bond character between the two

forms. Accordingly, the 1170-1145 cm^{-1} and 1145-1130 cm^{-1} regions were taken to represent the amido and imido forms respectively. An analogous phenomenon has been reported for the carbonyl absorption. Sheinker (66) found that in fixed imino compounds the carbonyl band was observed in the 1630-1605 cm^{-1} region, being substantially shifted from the 1718-1686 cm^{-1} position in the corresponding amino compound. Corroboration of the above was obtained from a comparison of the carbonyl absorption in acetazolamide and methazolamide (67).

By examining the relative positions of the SO_2 symmetric stretching frequencies, Uno et al. (64) found that N-(2-pyrimidinyl)-sulfonamide derivatives take on the amido form while N-(2-pyridyl) and N-(2-thiazolyl)-sulfonamide derivatives take on the imido form.

Similarly, Moskalyk and Chatten (1) assigned structures to their xanthenyl derivatives of sulfanilamides employing the regions 1160-1145 cm^{-1} and 1145-1130 cm^{-1} as representing the amido and imido forms, respectively. Their success with these regions further substantiated the utility of the relative positions of the SO_2 stretching frequencies for characterizing these tautomers.

In a publication following Moskalyk's work, Uno and coworkers (65) reported that 2-sulfonamidothiadiazoles existed in the imido form, while 3- and 5-sulfonamidoisoxazoles existed in the amido form, in the solid state. These conclusions were derived from the pattern of the spectral changes on N-deuteration

and a comparison with the corresponding carboxylic acid amides in the region 1650-1500 cm^{-1}. The relative positions of the SO_2 symmetrical stretching vibrations of the corresponding sulfanilamides showed these to take the same form as the benzenesulfonamides.

As was the case for the xanthenyl derivatives, the use of the bands in the 1050 to 850 cm^{-1} region to distinguish the imido from the amido form, as proposed by Sheinker et al. (62), could not be employed as the spectra of benzhydrol itself possesses several bands in this region. The relative number of maxima exhibited in the ultraviolet region could not be employed to distinguish these forms either, since the ultraviolet spectrum of benzhydrol is even more complicated than that of xanthydrol. This method has been successfully employed for this purpose when alkylation was carried out with simple alkyl groups such as the methyl radical (61).

Examination of the infrared spectrum of benzhydrol revealed that, not unlike xanthydrol, no strong absorptions occurred in the 1160-1125 cm^{-1} regions of the spectrum. Accordingly, the identical 1160-1145 cm^{-1} and 1145-1125 cm^{-1} regions were employed to represent the amido and the imido forms, respectively. As may be seen from Table IV, the band positions of these two derivatives do in fact fall into the lower region ascribed to the imido form, and thus, coupled with their failure to titrate, the presence of but a single band in the amino stretching regions of the infrared spectrum and the negative tests with furfural,

TABLE IV

Comparison of the SO_2 Symmetric Stretching Frequencies of the Benzhydrylsulfanilamides with those of the Previously Reported Xanthenylsulfanilamides (1)

Ref. No.[a]		SO_2 Symmetric Stretching (cm^{-1})		
		Parent[b]	Xanthenyl Derivative[b]	Benzhydryl Derivative
2	Sulfadiazine	1153	1148	1163
3	Sulfapyridine	1122	1127	1136
4	Sulfamerazine	1147	1147	1160
5	Sulfamethazine	1144	1152	1153
6	Sulfamethizole	1126[c]	1139[d]	1134
6d	Sulfamethizole	1126	-	1130
6bx	Sulfamethizole	1126	-	1130
7	Sulfachloropyridazine	1144	1134[d]	1147
7bx	Sulfachloropyridazine	1144	-	1136
8	Sulfamethoxypyridazine	1153[e]	1133[d]	1152
8bx	Sulfamethoxypyridazine	1153[e]	-	1124
9	Sulfacetamide	1148	1147	1160
10	Sulfaguanidine	1127	1133	1133
11	Sulfaphenazole	1148	1155	1152
12	Sulfaquinoxaline	1147	-	1155
13	Sulfanilanilide	1149	-	1143

continued

(TABLE IV (continued)

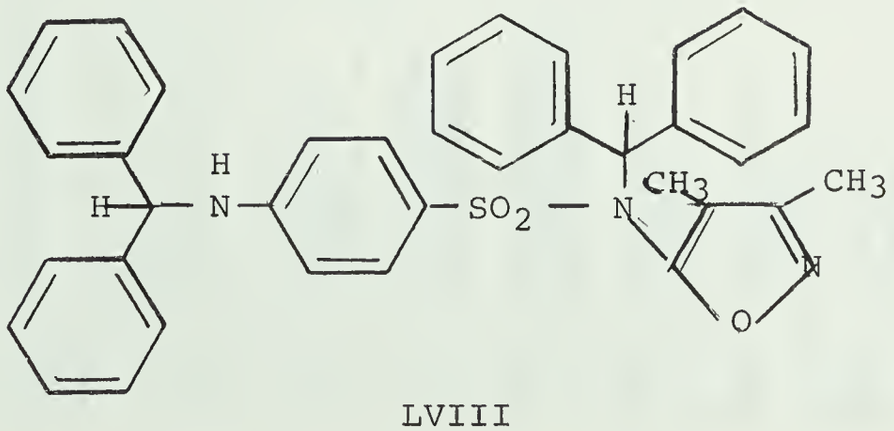
13d	Sulfanilanilide	1149	-	1143
13d'	Sulfanilanilide	1149	-	1149
14	Sulfamethoxazole	1154	1159	1160
15	Sulfadimethoxine	1142	1152[df]	1142[f]
15t	Sulfadimethoxine	1142	-	1163
15bx	Sulfadimethozine	1142	-	1142
16	Sulfaproxyline	1151	1151	1152
17	Sulfisoxazole	1159	1147[dg]	1149
17d	Sulfisoxazole	1159	-	1147
17bx	Sulfisoxazole	1159	-	1149
18	Sulfathiazole	1134	1135[d]	1139
18bx	Sulfathiazole	1134	-	1142
19	Sulfaethylthiadiazole	1140	1140[d]	1136
19d	Sulfaethylthiadiazole	1140	-	1130
19bx	Sulfaethylthiadiazole	1140	-	1132

a - bx refers to a benzhydryl-xanthenyl derivative
b - taken from (1), except compounds 12 and 13
c - shoulder at 1143 cm^{-1}
d - the derivatives are substituted twice with xanthydrol
e - weak band at 1126 cm^{-1}
f - shoulder at 1149 cm^{-1}
g - weak band at 1159 cm^{-1}

the structures illustrated by LIV and LV may be assigned to the dibenzhydryl derivatives of sulfamethizole and sulfaethylthiadiazole, respectively.

Further evidence for the correctness of the assignments came from the reaction of the monobenzhydryl derivatives (ref. nos. 6 and 19) with xanthydrol, in glacial acetic acid, to give the monoxanthenyl derivatives 6bx and 19bx, respectively (Table V). These monobenzhydryl-monoxanthenyl derivatives displayed their SO_2 stretching frequencies at the correspondingly low values of 1130 and 1132 cm^{-1}, respectively. These positions agree favourably with the 1130 cm^{-1} position for both of their dibenzhydryl derivatives (Table IV).

The last of the sulfanilamides in common to afford a dibenzhydryl derivative was that of sulfisoxazole (ref. no. 17d). For the corresponding xanthenyl derivative, Moskalyk and Chatten (1) proposed the amido substituted product. Thus, if the sites of substitution were identical, the compound with benzhydrol would be that represented by LVIII.



LVIII

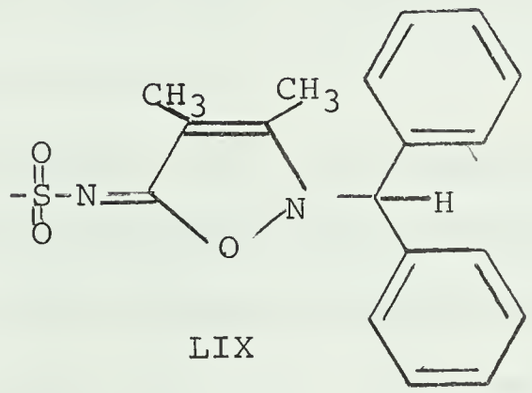
TABLE V

Monoxanthenyl Derivatives of N^4-Benzhydryl-N^1-Monosubstituted Sulfanilamides

Ref. No.[a]	N^4-Benzhydryl derivative of	Melting Point	Recrystallizing solvent	Formula	Analysis Calculated C	H	N	Found C	H	N
1bx	Sulfanilamide	245-245.5	Acetone-water	$C_{32}H_{26}N_2O_3S$	74.11	5.05	5.40	74.16	5.28	5.63
6bx	Sulfamethizole	253-253.5	Dioxane-water	$C_{35}H_{28}N_4O_3S_2$	68.16	4.58	9.08	69.68[b]	5.34	8.82
7bx	Sulfachloropyridazine	216-218	Dioxane-water	$C_{36}H_{27}ClN_4O_3S$	68.50	4.31	8.88	68.29	4.25	9.22
8bx	Sulfamethoxypyridazine	223.5-224	Chloroform-hexane	$C_{37}H_{30}N_4O_4S$	70.90	4.83	8.94	68.92[b]	4.75	8.50
15bx	Sulfadimethoxine	174-177	Chloroform-hexane	$C_{38}H_{32}N_4O_5S$	69.49	4.91	8.53	67.68[b]	4.92	8.10
17bx	Sulfisoxazole	184-185	Acetone-water	$C_{37}H_{31}N_3O_4S$	72.41	5.09	6.85	71.45[b]	5.16	7.07
18bx	Sulfathiazole	211.5-212	Acetone-water	$C_{35}H_{27}N_3O_3S_2$	69.86	4.50	6.97	69.78	4.71	6.55
19bx	Sulfaethylthiadiazole	204-205.5	Acetone-water	$C_{35}H_{30}N_4O_3S_2$	67.94	4.89	9.05	67.66	4.86	9.31

a - bx refers to a benzhydryl-xanthenyl derivative
b - these compounds could not be purified further

This sulfanilamide, as pointed out by these latter workers, differs from the other sulfanilamides encountered in this study, in several important ways. The amide hydrogen in this compound has been shown to be considerably more reactive than in other sulfanilamides, since it readily undergoes selective N^1 acetylation (68). (The N^1-acetyl derivative is a commercially available bacteriostatic sulfanilamide). Secondly, prototropic tautomerism in this sulfanilamide differs from that seen in the case of the thiadiazole sulfanilamides in that the annular nitrogen atom is now considerably removed from the extra ring nitrogen. Condensation from the imido form of this sulfanilamide would have yielded a compound with an extended conjugation (LIX), and in view of similar findings with the derivatives of sulfachloropyridazine and its methoxy homolog, a coloured product would be expected (1).



LIX

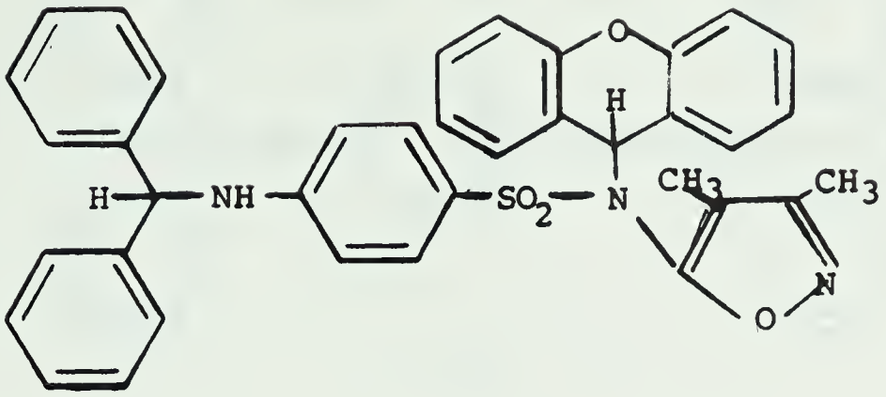
Since the product they isolated was white, they interpreted the relatively high position of the SO_2 symmetric stretching frequency (1147 cm^{-1}) to favor the amido form. In support of this structure, Boulton and Katritzky (69) from infrared and

nuclear magnetic resonance studies found the 5-amino as well as 5-acetamido-isoxazoles existed predominantly in the amino or amido state. As mentioned previously, Uno et al. (65) have since reported that 3- and 5-sulfonamido-isoxazoles exist in the amido form in the solid state, lending further support to the structural assignment made by these workers for the xanthenyl derivative of sulfisoxazole.

The disubstituted product isolated with benzhydrol in this study was similarly white in colour, it failed to titrate and it exhibited the SO_2 symmetric stretching frequency at the identical position of 1147 cm^{-1}. Furthermore, condensation of the N^4-monobenzhydryl derivative (ref. no. 17) with xanthydrol, according to Moskalyk's procedure, afforded a monobenzhydryl-monoxanthenyl derivative (ref. no. 17bx) (Table V) which displayed its SO_2 symmetric stretching frequency at nearly the same position (1149 cm^{-1}) (Table IV). This product was similarly white, and failed to titrate.

Thus, it would appear that the dibenzhydryl derivative (ref. no. 17d) of sulfisoxazole may be correctly represented by the structure LVIII. The xanthenyl moiety in the corresponding monoxanthenyl derivative (ref. no. 17bx) would thus be expected to occupy the identical N^1-position (LX).

In addition to the three sulfanilamides which afforded dibenzhydryl derivatives, Moskalyk and Chatten (1) obtained dixanthenyl derivatives with sulfanilamide, sulfachloropyridazine, sulfamethoxypyridazine and sulfathiazole. Attempts at

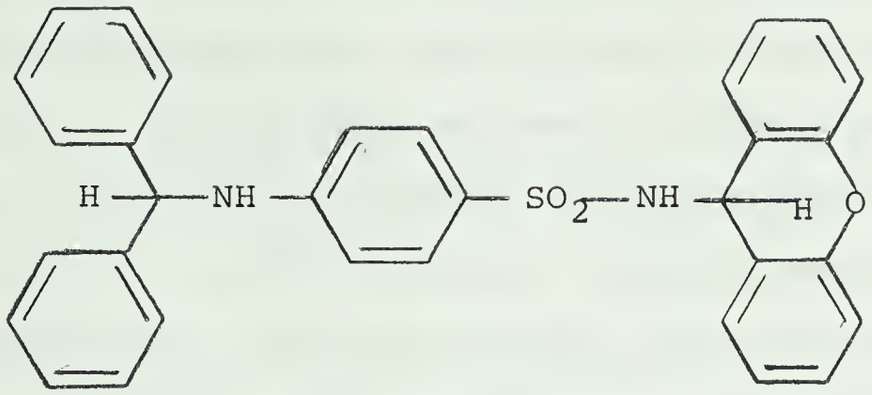


LX

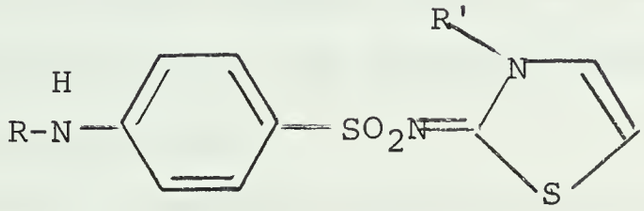
obtaining the dibenzhydryl derivatives with these sulfanilamides failed. To ascertain whether or not the second sites of substitution in these compounds were still available to react with xanthydrol, the N^4-benzhydryl derivatives of each of these sulfanilamides were treated further with a mole of xanthydrol. As may be seen from Table V, each of these sulfanilamides afforded the corresponding monobenzhydryl-monoxanthenyl derivatives.

By analogy with the dixanthenyl derivative (1), the product with sulfanilamide (ref. no 1bx) must be that illustrated by structure LXI.

Sulfathiazole itself (LXII) has been shown to exist in the imido tautomeric form (61, 62, 64, 66). The structure assigned to the dixanthenyl derivative was that given by LXIII.



LXI



LXII (R = R' = H)

LXIII (R = R' = xanthenyl)

LXIV (R = benzhydryl, R' = xanthenyl)

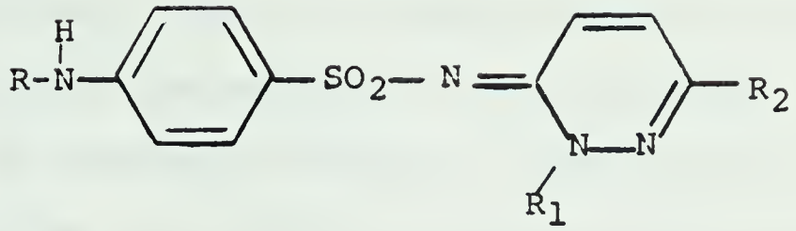
Proof for this structure included its inability to titrate and the appearance of the SO_2 symmetric stretching frequency at 1135 cm^{-1} as compared with 1134 cm^{-1} for the parent compound. The compound in question (ref. no. 18bx) also failed to titrate, and the SO_2 symmetric stretching frequency appeared in the lower frequency region (1142 cm^{-1}). Accordingly, the monobenzhydryl-monoxanthenyl derivative of sulfathiazole may be assigned

the structure illustrated by LXIV.

Sulfachloropyridazine and sulfamethoxypyridazine were found to give the dixanthenyl derivatives LXV and LXVI, respectively (1). The authors arrived at these structural assignments on the basis of several considerations including their inability to titrate and their infrared characteristics. Sulfachloropyridazine exhibited its SO_2 symmetric stretching frequency at 1144 cm^{-1}, while the dixanthenyl derivative (LXV) showed the peak at 1134 cm^{-1}. A more dramatic shift occurred with the methoxy homolog (1153 cm^{-1} to 1133 cm^{-1}). Both of the above compounds afforded coloured (yellow) derivatives which the authors attributed to the resulting extension of the conjugation in the molecule.

Reaction of the N^4-benzhydryl derivatives of sulfachloropyridazine and sulfamethoxypyridazine with xanthydrol also yielded yellow derivatives in both instances. The SO_2 symmetric stretching frequencies likewise appeared at the comparably low positions of 1136 cm^{-1} and 1124 cm^{-1}, respectively. Therefore, the structures of the monobenzhydryl-monoxanthenyl derivatives of the chloro (ref. no. 7bx) and methoxy (ref. no. 8bx) analogs can be represented by structures LXVII and LXVIII respectively.

It should be pointed out at this time that each of the monoxanthenyl derivatives prepared from the corresponding N^4-monobenzhydrylsulfanilamides were stable compounds which could be readily purified by recrystallization in the normal manner. This observation supports the several similar



LXV (R = R_1 = xanthenyl, R_2 = Cl)
LXVI (R = R_1 = xanthenyl, R_2 = OCH_3)
LXVII (R = benzhydryl, R_1 = xanthenyl, R_2 = Cl)
LXVIII (R = benzhydryl, R_1 = xanthenyl, R_2 = OCH_3)

observations made by Moskalyk and Chatten (1) which led them to conclude that the instability of the xanthenyl derivatives which they isolated was associated with the N^4-bond and that the second xanthenyl moiety formed a stronger and more stable bond.

Although Moskalyk and Chatten (1) obtained only a monosubstituted derivative with sulfanilanilide, two different dibenzhydryl derivatives (ref. nos. 13d and 13d') were isolated when this sulfanilamide was treated with a two molar ratio of benzhydrol. Since the monobenzhydryl and monoxanthenyl derivatives of sulfanilanilide were shown to be substituted at the N^4-position, it was expected that one or both of the disubstituted products would be similarly substituted.

Examination of the infrared spectra revealed that compound 13d exhibited two peaks in the amino stretching region (3484 and 3361 cm^{-1}), while compound 13d' displayed but a single band at 3333 cm^{-1}. Both compounds nonetheless failed to respond to the furfural test.

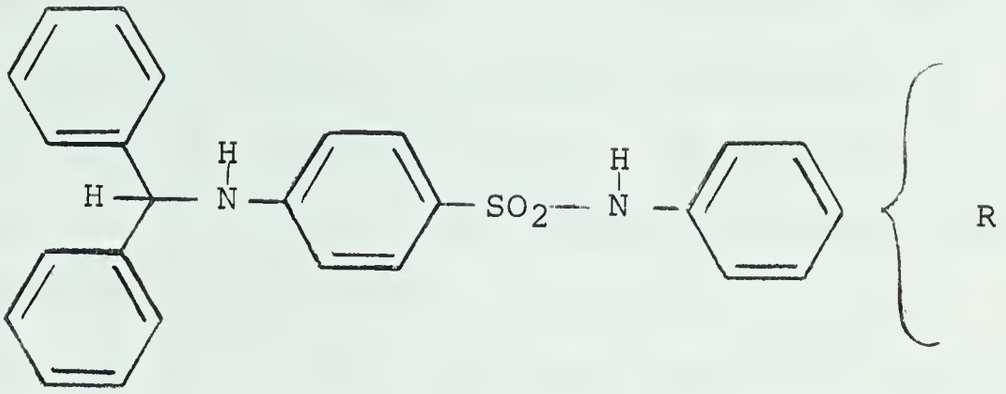
Although the results of the furfural test did not agree with the infrared evidence, supporting the primary amino structure, for compound 13d the negative test could be the result of steric interference from the neighbouring bulky diphenylmethyl group, thereby preventing the close approach of the amino group to the furfural molecule. This postulate was substantiated by the negative tests obtained with several sulfanilamides which possessed bromine atoms at the two positions ortho to the amino group.

Thus compound 13d' is the N^4-substituted derivative and possesses the partial structure given by LXIX, whereas 13d likely carried one of the benzhydryl moieties in the position ortho to the amino group (LXX).

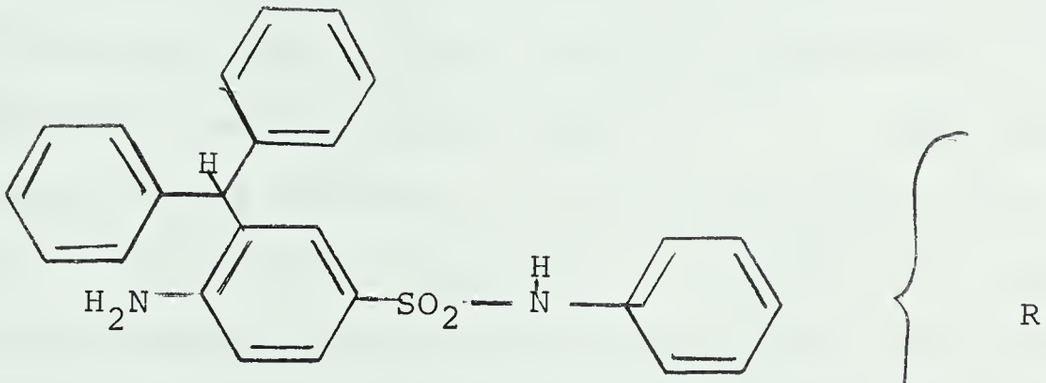
The probability of the second site being a common one was now certainly indicated.

Three sites were considered possible for the second benzhydryl radical. These were the remaining position ortho to the amino group, on the amide nitrogen, or on the benzene ring located at the N^1 position. Both compounds failed to titrate, which would support substitution of the amide hydrogen, however, the monobenzhydryl derivative of sulfanilamide (ref. no. 13) also failed to titrate for some unexplainable reason.

In an attempt to obtain additional information as to the site of condensation of the second alkyl group, a 60 Mc. nuclear magnetic resonance spectrum in dimethylsulfoxide was obtained for the derivatives as well as the parent sulfanilamide.



LXIX (R = benzhydryl)



LXX (R = benzhydryl)

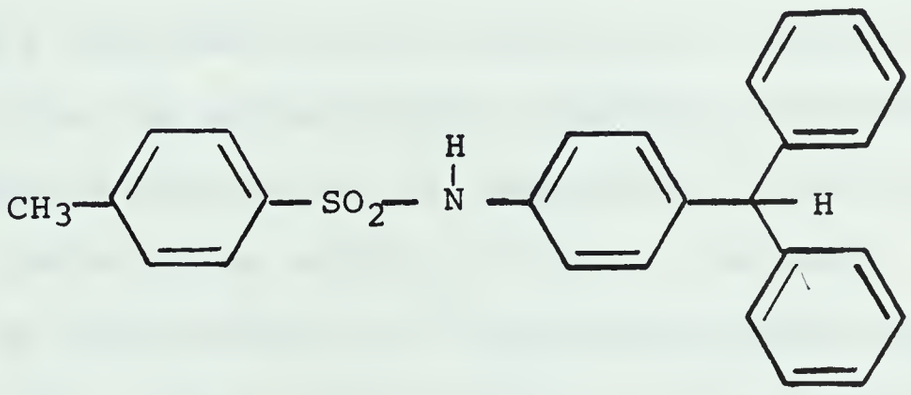
Examination of the spectrum of compound 13d revealed a broad peak at τ4.8, accounting for two protons; a sharper absorption at τ4.4, also accounting for two protons and a sharp singlet at τ0.3 which accounted for only a single proton. In addition, a complex pattern was displayed in the aromatic region. The spectrum of sulfanilanilide itself displayed a one proton singlet at τ0.2; a slightly broadened two proton signal at τ4.12, in addition to nine protons in the aromatic region.

The interpretation of the latter spectrum presented no difficulty. The one proton signal at τ0.2 must be the amide proton while the two proton signal at τ4.12 must be the two amino protons; the nine remaining protons are aromatic in nature and fall into the expected region. The spectrum of the derivative (ref. no. 13d) should have retained the two amino peaks which could be accounted for by the peak at either τ4.8 or τ4.4. Since one of the last mentioned peaks was not present in the spectrum of the parent sulfanilamide, one of these peaks must account for the α protons on each of the benzhydryl substituents. This low field absorption would not be surprising in view of the fact that these protons are adjacent to the two electron-withdrawing phenyl rings. Since the spectrum of derivative 13d displayed a single proton signal at τ0.3, this must be due to the amide proton because it is the only source of a single proton. Although the spectrum of compound 13d' was not as well defined, nonetheless it did display a one proton signal at the identical position of τ0.3. Also this position agrees with the amide absorption signal at τ0.2 in the parent compound. Utilization of the aromatic region proved impractical due to the complexity of the region containing 23 protons.

In accord with the spectral data, the amide hydrogen must still be present in both compound 13d and 13d', and thus contrary to the titration data, substitution did not occur at the N^1- nitrogen atom.

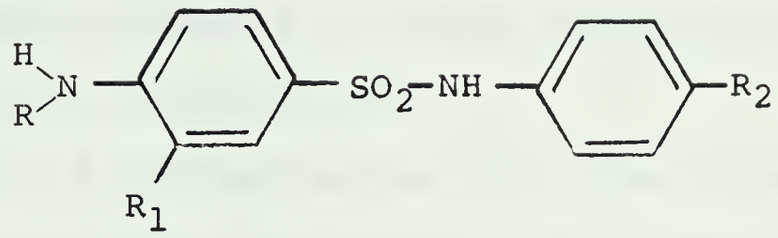
In an attempt to differentiate the remaining two possibilities,

N-phenyl-p-toluenesulfonamide was prepared by the reaction of aniline with p-toluenesulfonyl chloride (70). This compound was then treated under similar conditions to those used to obtain the disubstituted sulfanilanilide (ref. no. 13d). Since Cheeseman (19) obtained only a monosubstituted derivative with p-toluenesulfonamide, no substitution would be expected on the tolyl ring and thus the only potentially reactive position should be the phenyl ring attached to the amide nitrogen. The product obtained from this reaction was found to be the corresponding monobenzhydryl derivative. In view of the fact that the para position is the most active and the least hindered position, the most likely structure of the monobenzhydryl derivative is that given by LXXI.



LXXI

By analogy, the dibenzhydrylsulfanilanilide (ref. no. 13d) must be that shown by structure LXXII, and compound 13d' must be that represented by LXXIII.



LXXII (R = H, R_1 = R_2 = benzhydryl)

LXXIII (R_1 = H, R = R_2 = benzhydryl)

To further substantiate the validity of the latter structural assignments, the compounds were brominated. Since sulfanilanilide should brominate at the two positions ortho to the amino group, then if structure LXXII is correctly assigned for compound 13d, it should take up only a single bromine atom. The product isolated from the bromination reaction analyzed correctly for the corresponding monobromo derivative.

Attempted bromination of compound 13d' proved unsuccessful and only the starting material could be isolated. Similar attempts at bromination of N^4-benzhydrylsulfanilanilide (ref. no. 13), also failed. On this basis, it was concluded that these positions, under the conditions of the reaction, were sterically hindered by the bulky diphenylmethyl group and therefore would not brominate.

N-phenyl-p-toluenesulfonamide was also treated with benzhydrol under the milder reaction conditions which yielded compound 13d'. The product isolated from the reaction was

found, from a mixed melting point determination and its infrared spectrum, to be identical to compound LXXI isolated previously under the more drastic reaction conditions. It therefore seemed reasonable to assume that structure LXXIII is correct for the compound 13d'.

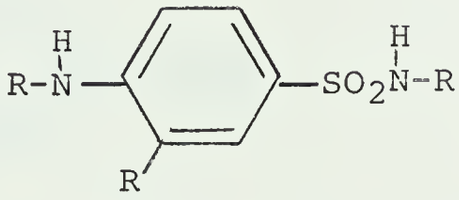
Hydrolysis of the derivative (13d') was attempted employing 40% hydrogen bromide and phenol (71), however, no products could be isolated from the reaction mixture.

Tribenzhydryl Derivatives

The compound isolated from the reaction of a two-to-one molar ratio of benzhydrol to sulfanilamide turned out to be a trisubstituted derivative. It will be recalled that the product from a equimolar reaction was the corresponding N^4-monosubstituted compound. A disubstituted product could not be obtained by this method.

An examination of the infrared spectrum of the compound established the N^4-position as one of the sites of substitution. Whereas sulfanilamide itself exhibits bands at 3430 and 3305 cm^{-1} (1), the derivative displayed but a single band at 3425 cm^{-1}. The test with furfural also proved to be negative. Since published data has established the reactivity of primary sulfonamides with benzhydrol, as well as xanthydrol, this site would also be expected to be substituted. The reaction with xanthydrol, for example, afforded the N^1, N^4-dixanthenyl derivative (1). Furthermore, in view of the fact that disub-

stitution at either N^1 or N^4 has not been previously encountered, it would appear that the most logical site for the third benzhydryl moiety would be on the benzene ring, as shown by structure LXXIV .



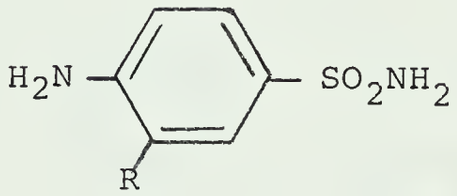
LXXIV , (R = benzhydryl)

Because of the complexity of the structure, physical methods, including infrared and nuclear magnetic resonance spectroscopy, could not be employed to verify this type of substitution. Thus, an attempt was made to hydrolyze the derivative in the hope of being able to identify the subsequent products. The compound was refluxed with 48% hydrobromic acid and phenol according to the method of Snyder and Heckert (71). This is a more satisfactory procedure for hydrolyzing sulfonamides and is not simply hydrolysis, but is a reductive cleavage in which the sulfonamide is reduced to the disulfide (equation 14).

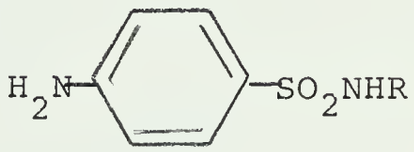
$$2\ ArSO_2NR_2 + 5HBr + 5C_6H_5OH \rightarrow ArSSAr + 2R_2NH + 5BrC_6H_4OH + 4H_2O \quad (14)$$

The only product which could be isolated from this reaction was not the expected product, but actually a monobenzhydrylsulfanilamide. This product was not the N^4-monosubstituted compound

previously prepared. Its infrared spectrum displayed two bands in the amino stretching region signifying that the N^4-nitrogen was unsubstituted. Thus, the product was most likely that illustrated by LXXV or LXXVI.



LXXV



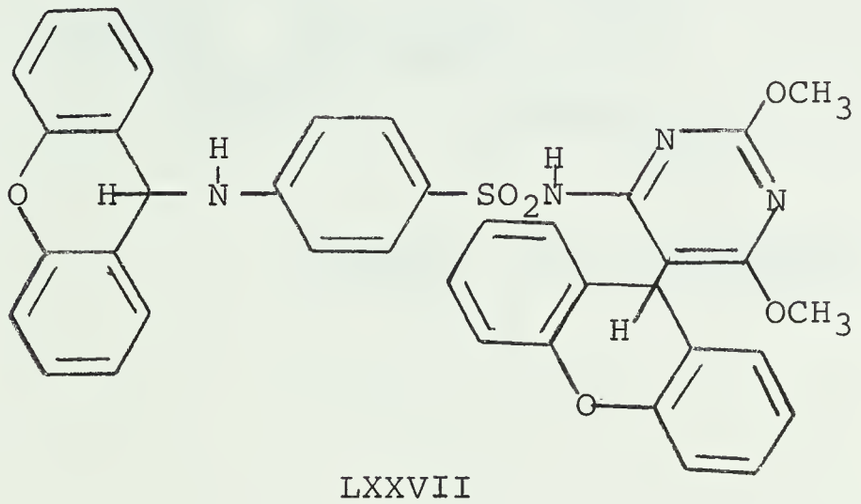
(R = benzhydryl) LXXVI

These may be distinguished readily by bromination. Since sulfanilamide itself is known to yield the corresponding 3,5-dibromo derivative (72), compound LXXV should yield a monobromo derivative, whereas LXXVI would be expected to yield a dibromo compound. Bromination afforded a compound whose elemental analysis agreed with a monobromo derivative, and thus the product isolated from the hydrolysis must be that given by LXXV. Attempts at brominating the trisubstituted product failed. However, similar results were obtained previously when the N^4-position was substituted with a benzhydryl group.

It would thus appear that the alkaline hydrolysis reaction attempted, served to cleave the two C-N bonds at N^1 and N^4, but the C-C bond was resistant to such treatment. The more stable nature of the latter type of bond has been observed previously with xanthenyl derivatives (1, 73). Based on the aforementioned

evidence, the trisubstituted derivative isolated must be that given by LXXIV.

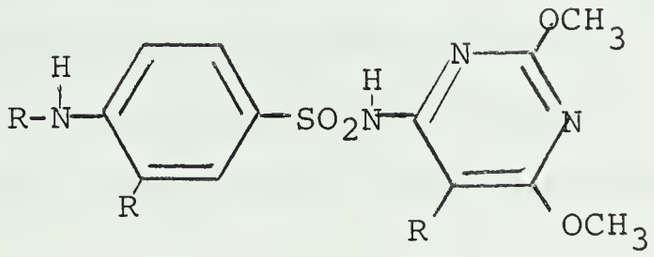
The only other sulfanilamide to yield a trisubstituted derivative with benzhydrol was sulfadimethoxine (ref. no. 15t). With xanthydrol, it yielded the dixanthenyl derivative LXXVII (1).



LXXVII

The compound in question failed to react with furfural reagent and displayed but one band in the amino stretching region, establishing the N^4-position as one of the sites of substitution. The presence of the amide hydrogen was demonstrated by its titratability in a nonaqueous solvent. Since the 5-position of the pyrimidine ring has been shown to be particularly reactive towards electrophilic substitution, when the 2 and 4 positions are occupied by strongly ortho-para directing groups (74), it would appear likely that this would constitute the second site of substitution. As there are no remaining available reactive sites, except for the 3 position of the sulfanilamide molecule, the structure of the tribenzhydryl

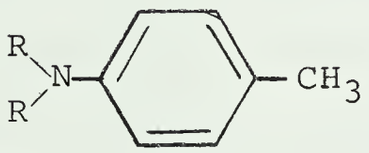
derivative of sulfadimethoxine (ref. no. 15t) must be that given by LXXVIII.



LXXVIII (R = benzhydryl)

Reaction Products Obtained by Fusion in the Presence of Zinc Chloride

A unique substitution pattern resulting from the reaction of benzhydrol with para substituted anilines has been reported by Cantarel (43) and Giraud (44). These workers reported that fusion, in the presence of zinc chloride, afforded the corresponding N,N-dibenzhydryl derivatives. For example, with p-toluidine they obtained the compound illustrated by LXXIX.



LXXIX (R = benzhydryl)

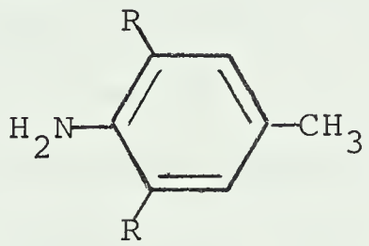
Since the sulfanilamides involved in this study are in fact para substituted anilines, similar products would be expected under the same reaction conditions.

The physical properties of the first few products isolated by this procedure did not appear to correspond to the structure proposed by these workers. Accordingly, the reaction with p-toluidine, as reported by Giraud (44), was re-examined. He reported isolating a product melting at 188°C. Upon duplicating his procedure, a compound with an identical melting point was isolated. Elemental analysis verified that the compound was in fact the disubstituted derivative. Although this product did not give a positive test with furfural reagent,

the infrared spectrum still exhibited two peaks in the amino stretching region. These peaks appeared depressed in intensity. In order to ascertain whether these depressed peaks did represent the two unsubstituted amino protons, a 60 Mc nuclear magnetic resonance spectrum was recorded in dimethylsulfoxide on both the parent compound and the corresponding derivative. The spectrum of p-toluidine exhibited the expected AB coupling pattern in the aromatic region. In addition, it exhibited a two proton signal at τ6.78, which was assigned to the amino protons, and a three proton methyl signal which appeared at τ7.84. Examination of the spectrum of the corresponding derivative revealed a three proton singlet at τ8.05, which was attributed to the methyl group, and two signals each accounting for two protons at τ6.97 and τ4.72. One of these latter signals must be attributed to the hydrogens on the α carbon on each of the benzhydryl substituents. The low field position of the signal was not alarming, since it is adjacent to the two electron-withdrawing phenyl groups. The only other possible two proton group which could account for the other signal at this field position is the amino group. This position corresponded very closely to the position of the signal of the amino group in the spectrum of p-toluidine. Although a deuterium exchange was not performed to distinguish the latter two signals, the presence of these signals showed without a doubt that the benzhydryl groups had substituted on the aromatic nucleus. The most logical positions for

substitution to have taken place are the two positions ortho to the ortho-para directing amino group.

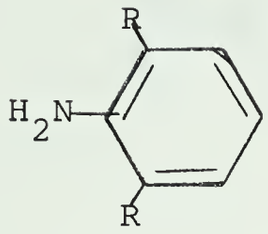
In view of the aforementioned evidence, it was concluded that the structure for the p-toluidine derivative assigned by Giraud was in fact incorrect, and that the correct assignment was that given by structure LXXX.



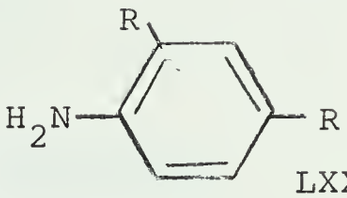
LXXX (R = benzhydryl)

The remainder of the structural assignments proposed by Giraud would now appear to be in doubt.

When sulfacetamide was fused with benzhydrol, in the presence of zinc chloride, a product was isolated which demonstrated no carbonyl or sulfonyl absorption in the infrared region. The elemental analysis corresponded to a dibenzhydryl derivative of aniline. Two peaks were evident in the amino stretching region, suggesting ring substitution. However, unlike the p-toluidine derivative this compound had an additional unoccupied ring position resulting from the cleavage of the C-S bond and subsequent elimination of $-SO_2NHCOCH_3$. Therefore, the structure for this derivative must be that represented by either LXXXI or LXXXII, depending when cleavage of the $SO_2NHCOCH_3$ group occurred relative to alkylation.



LXXXI (R = benzhydryl)

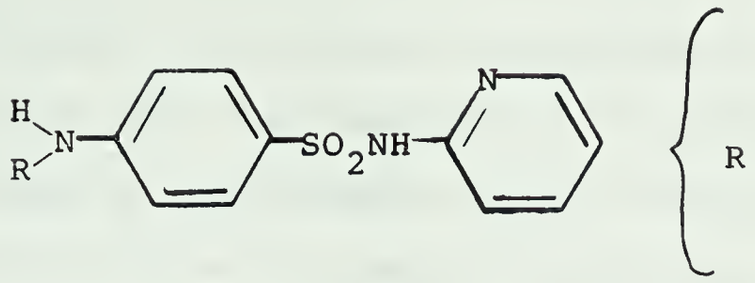


LXXXII

Other than the depressed amino peaks in the infrared spectrum, additional evidence as to the pattern of substitution from other physical tools such as nuclear magnetic resonance spectroscopy proved of little value because of the complicating effect of the four phenyl groups of the two benzhydryl substituents. However, in view of the fact that nuclear substituted dibenzhydryl derivatives resulted with a number of p-substituted anilines, the former assignment (LXXXI) would appear to be the favored one.

Sulfapyridine, on reaction under the same conditions, failed to yield a derivative. However, heating for a shorter period of time yielded a white crystalline material whose elemental analysis corresponded to a disubstituted derivative. The product gave a negative furfural test, but the infrared spectrum displayed but a single band in the amino stretching region characteristic of N^4-substitution. The partial structure of the derivative can therefore be represented by structure LXXXIII.

Further examination of the infrared spectrum revealed that the SO_2 symmetric stretching frequency appeared at 1147 cm^{-1},



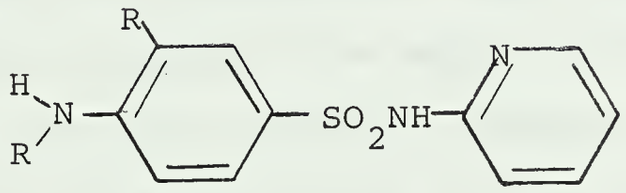
LXXXIII (R = benzhydryl)

which suggested that the compound existed in the amido tautomeric form. The ability of the derivative to titrate confirmed the presence of the amide hydrogen. This latter evidence also discounted the possibility of substitution on the annular nitrogen atom via the imido tautomer. Since dibenzhydryl or dixanthenyl derivatives have not been previously isolated with this sulfanilamide, this would tend to minimize the possibility of substitution on the pyridine ring.

Sulfapyridine is known to brominate in the two positions ortho to the amino group (75). In an attempt to ascertain the site of substitution of the second mole of benzhydrol, the dibromo compound was prepared and treated under the same conditions which yielded the dibenzhydryl derivative. The compond isolated from the reaction proved to be the starting material.

The bromine atoms, although large, are significantly far removed from the pyridine ring that steric interference from these groups would not be expected to prevent reaction on the pyridine ring, if this was the reactive site. Previous work

with xanthydrol (1), as well as experience with benzhydrol has revealed that the reactivity of the N^4-nitrogen atom is destroyed by the presence of two ortho bromine atoms, undoubtedly because of steric interference. Thus, the failure of this compound to react would tend to imply that besides the N^4-position, the dibenzhydryl derivative of sulfapyridine must be substituted also in the ortho position as shown by structure LXXXIV.



LXXXIV (R = benzhydryl)

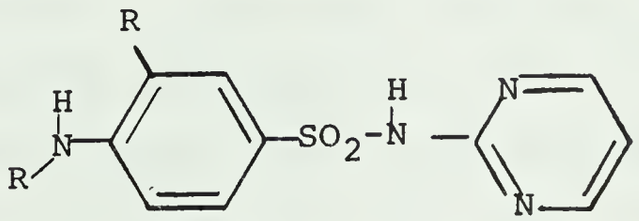
This is an analogous situation to that encountered with the trisubstituted derivatives of sulfanilamide (LXXIV), and sulfadimethoxine (LXXVIII).

Compound LXXXIV represents yet another type of substitution pattern possible by Giraud's method, and thus casts further doubt on the validity of his structural assignments.

Treatment of N^4-monobenzhydrylsulfapyridine (ref. no. 3) with benzhydrol under these fusion conditions afforded a product identical with LXXXIV, as evident from a mixed melting point determination and an identical infrared spectrum.

Sulfadiazine, also yielded a disubstituted derivative when fused with benzhydrol in the presence of zinc chloride.

This product also failed to react with furfural reagent. The infrared spectrum displayed only one peak in the amino stretching region, again typical of N^4-nitrogen substitution. The SO_2 stretching frequency appeared at 1163 cm^{-1} which suggested that the compounds existed in the amido form. The compound could be titrated as an acid, confirming the presence of the amide hydrogen. This latter evidence again eliminated the possibility of substitution on either of the annular nitrogen atoms via the imido tautomer. Reaction of the dibromo analog of this sulfanilamide with benzhydrol, under similar reaction conditions, yielded an amorphous gum which could not be crystallized. The preceding evidence suggested a similar conclusion regarding its substitution to that observed with sulfapyridine, and thus the product may be represented as shown by LXXXV.



LXXXV (R = benzhydryl)

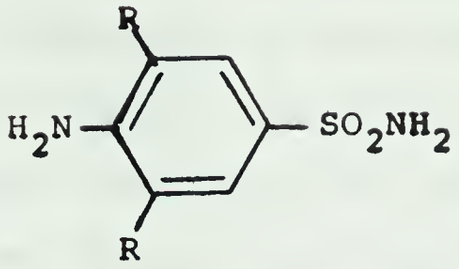
Fusing sulfanilanilide with benzhydrol, in the presence of zinc chloride, for a short period of time yielded a monosubstituted product in very low yield. The compound melted at a temperature identical with the N^4-monobenzhydryl derivative prepared earlier, and a mixed melting point and comparison

of the infrared spectra proved these compounds to be identical. Fusion for a longer period of time failed to yield a product.

Similarly, attempted fusions with sulfaquinoxaline, sulfamerazine, and sulfamethizole failed to yield derivatives under the reaction conditions employed by Giraud. However, derivatives of these sulfanilamides were isolated using lower fusion temperatures for shorter periods of time. In fact, the derivatives were shown to be the same as those isolated earlier employing perchloric acid as the catalyst, that is the corresponding N^4-monobenzhydryl derivatives. It would appear that the first step in alkylations by this fusion procedure may involve substitution of the N^4-nitrogen atom.

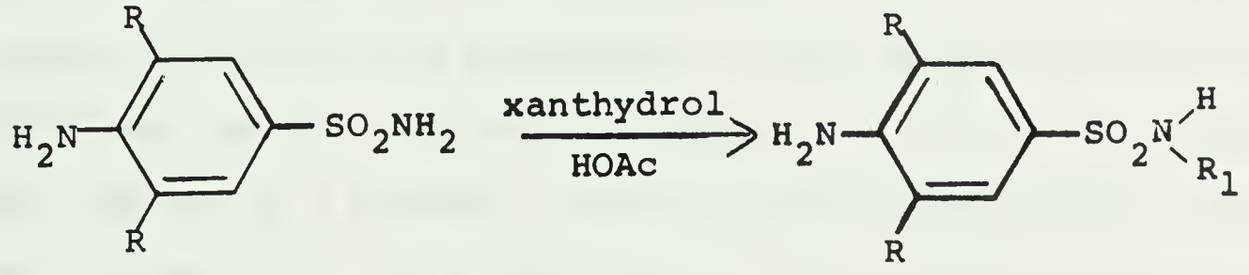
Fusing sulfanilamide at 180° with a two molar ratio of benzhydrol, in the presence of zinc chloride, afforded a dibenzhydryl derivative. It gave a negative test with furfural reagent. Examination of the infrared spectrum disclosed that in the region attributed to the amino stretching frequency, the derivative displayed three peaks at 3390 cm^{-1}, 3300 cm^{-1}, and 3205 cm^{-1}. Sulfanilamide itself displays three bands in this region at 3430, 3305 and 3210 cm^{-1}, the latter peak being due to the amide hydrogen (76). This spectral evidence would tend to suggest the structure shown by LXXXVI.

It was of interest to find that the derivative had retained the sulfamyl grouping, since with the acetyl analog (sulfacetamide), cleavage occurred to give the disubstituted aniline. Since these two sulfanilamides differ only by an acetyl group,



LXXXVI (R = benzhydryl)

this would tend to implicate this group as the driving force in the cleavage. Moskalyk and Chatten (1) have shown that sulfanilamide readily condensed at the N^1 and N^4 nitrogens, when reacted with xanthydrol. If the above structural assignment is correct, then by employing the method of these last mentioned workers, a monoxanthenyl derivative as shown by structure LXXXVII should be obtained.



LXXXVI (R = benzhydryl) (R_1 = xanthenyl) LXXXVII

Reacting LXXXVI with xanthydrol in acetic acid gave a product whose analysis corresponded to that calculated for LXXXVII.

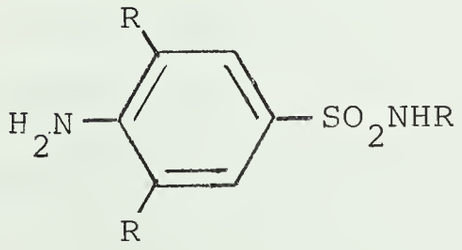
Although the dixanthenyl sulfanilamide was reported to be extremely unstable, this derivative proved to be very

stable and easily purified. Since it will be recalled that the instability was attributed to xanthenyl substitution at the N^4-nitrogen, the stability of the product isolated would tend to support the structural assignment (LXXXVII) made for this compound, and thus indirectly for LXXXVI.

Employing a three-to-one molar ratio of the alcohol to sulfanilamide, under similar reaction conditions, again yielded LXXXVI as the product. Similarly, a five-to-one molar ratio of benzhydrol to sulfanilamide yielded the aforementioned derivative. Since the excess benzhydrol failed to alkylate the N^1-position, and since it was shown to be active towards alkylation in prior experiments, the apparent inactivity of this site became of concern. Since alkylation proceeded at this position with xanthydrol, at room temperature, the possibility of the N^1-product cleaving under the conditions employed with benzhydrol was considered to be a distinct possibility. In an attempt to verify this postulate, a three molar ratio of benzhydrol was reacted with sulfanilamide at 100° for the relatively short period of 5 minutes. The trisubstituted product isolated from the reaction, in a high yield, had a melting point identical with the tribenzhydrylsulfanilamide (LXXIV) (ref. no. It) isolated earlier. A mixed melting point determination and infrared spectra comparison proved these compounds to be identical. This confirmed the instability of this group at higher temperatures, since N^1-substitution did take place at this lower temperature. To clarify the effects of temperature

on the isolated products, a three molar ratio of benzhydrol to sulfanilamide was fused at 160°. Two compounds were isolated from the reaction mixture. One had a melting point identical with LXXXVI, and was in fact shown to be the same compound by a mixed melting point determination and infrared spectral comparisons. The other product had a melting point different from any previously isolated derivatives of this sulfanilamide. The latter compound failed to react with furfural, and the elemental analysis corresponded to a tri-substituted derivative. Examination of the infrared spectrum revealed that unlike the spectrum of compound LXXXVI, only two bands were present in the amino stretching region at 3390 cm^{-1} and 3300 cm^{-1}. The band present in the parent compound at 3210 cm^{-1} had disappeared, indicating that amide substitution had occurred.

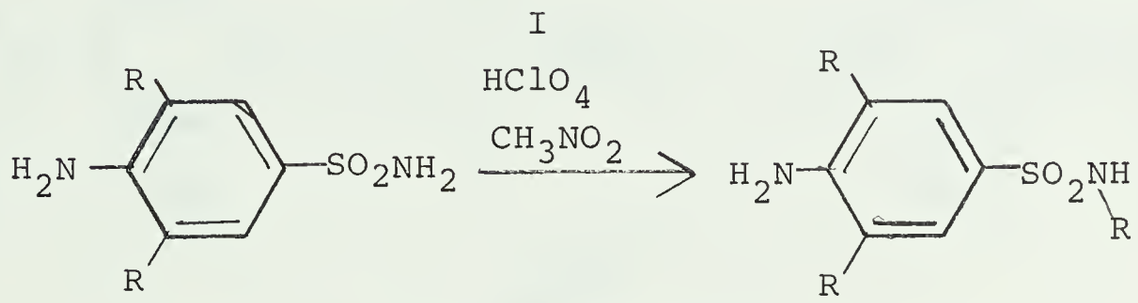
On this basis, this derivative must be that shown by LXXXVIII.



LXXXVIII (R = benzhydryl)

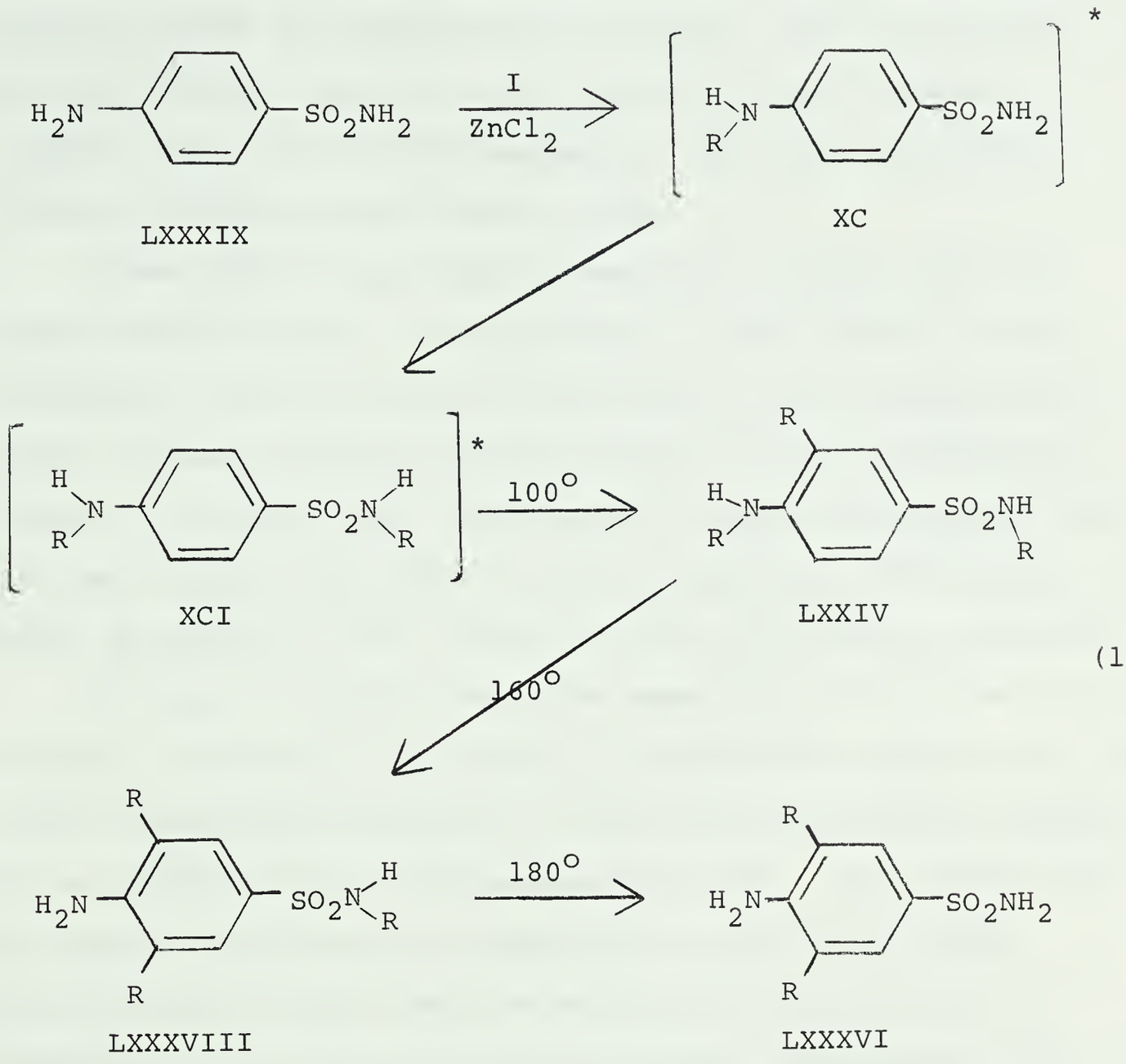
If structure LXXXVIII was correctly assigned, the same compound should result from the reaction of LXXXVI with benzhydrol in nitromethane and perchloric acid, since the N^1 site

was shown to be reactive under these conditions. On performing the reaction, a compound was isolated which, after purification, melted at the same temperature as LXXXVIII. A mixed melting point determination and comparison of the infrared spectra proved these compounds to be identical, thus validating the structural assignment for LXXXVIII, and indirectly for LXXXVI.



LXXXVI (R = benzhydryl) LXXXVIII

The isolation of the different reaction products at different temperatures suggested the sequence of steps for the reaction given by equation 15. Although compounds XC and XCI were not isolated, on the basis of previous evidence they would appear to be highly likely intermediates. Since sulfaquinoxaline, sulfamethizole, and sulfamethazine were shown to yield only monobenzhydryl derivatives when fused at low temperatures, it seems reasonable to assume that sulfanilamide would also produce the N^4-benzhydryl derivative as the first product in such a sequence. This is further supported from a consideration of the fact that sulfanilamide condenses at the N^4-site when reacted with a molar amount of



(15)

(R = benzhydryl)

* These intermediates were not isolated under fusion reaction conditions. Compound XC (ref. no. 1) was obtained by the general method.

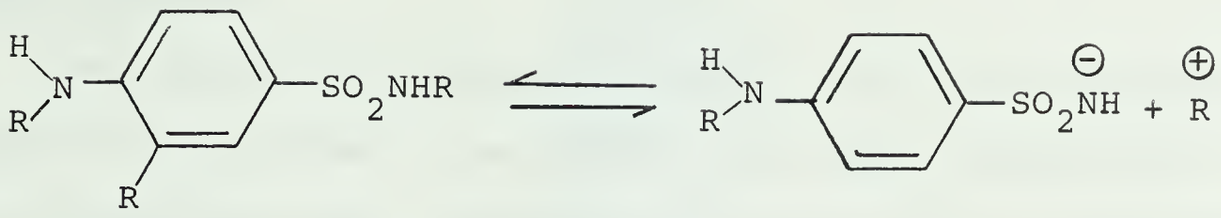
benzhydrol in a perchloric acid-nitromethane medium (ref. no. 1). The second suggested intermediate, XCI, would fit such a sequence since Moskalyk and Chatten (1) found that the

sulfanilamide derivative they isolated on reaction with xanthydrol showed this substitution pattern. Also, this site is less hindered than the ortho position, which further supports the order of this sequence. The third step would give the trisubstituted product LXXIV.

Since LXXXVIII and LXXXVI were both isolated from the same reaction mixture, it was evident that a shift of the benzhydryl moiety from the N^4-position to the corresponding ortho position occurred before cleavage of the N^1-benzhydryl group. It follows that the cleavage of the N^1-benzhydryl radical must be the final step in such a sequence, particularly since on fusing at 180°, LXXXVI is the only product isolated.

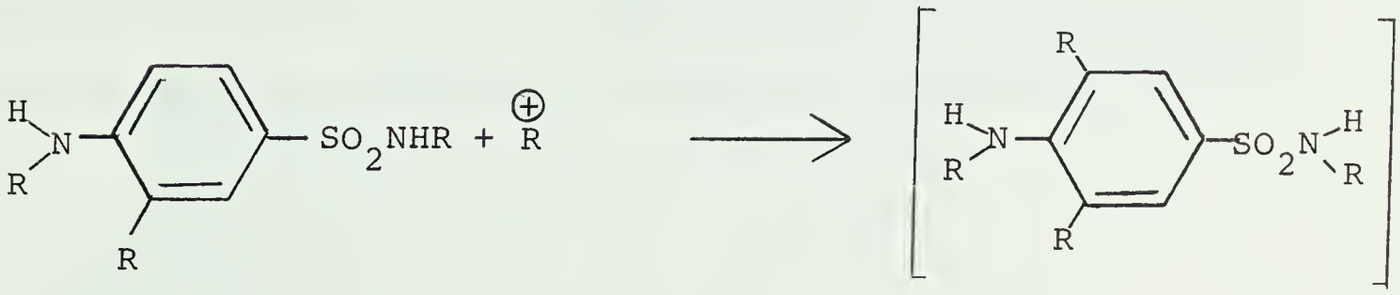
In view of the fact that the reactions were carried out without an excess of the alcohol, the apparent migration of the amino substituted benzhydryl to the ortho position was suspected to proceed via an intramolecular process. The possibility of some of the molecules fragmenting at the N^1 or the N^4-position, and in turn being attacked by LXXIV as shown by equation 16, to form the tetrasubstituted intermediate XCII, would appear unlikely because of extreme steric crowding. Preparation and examination of molecular models substantiated the latter statement.

It would thus appear that the N^4-benzhydryl group shifted before the other ortho position was substituted. The cleaved cation should therefore be free in solution to be attacked by another reactive site. If it is assumed that only molecules



LXXIV (R = benzhydryl)

(16)

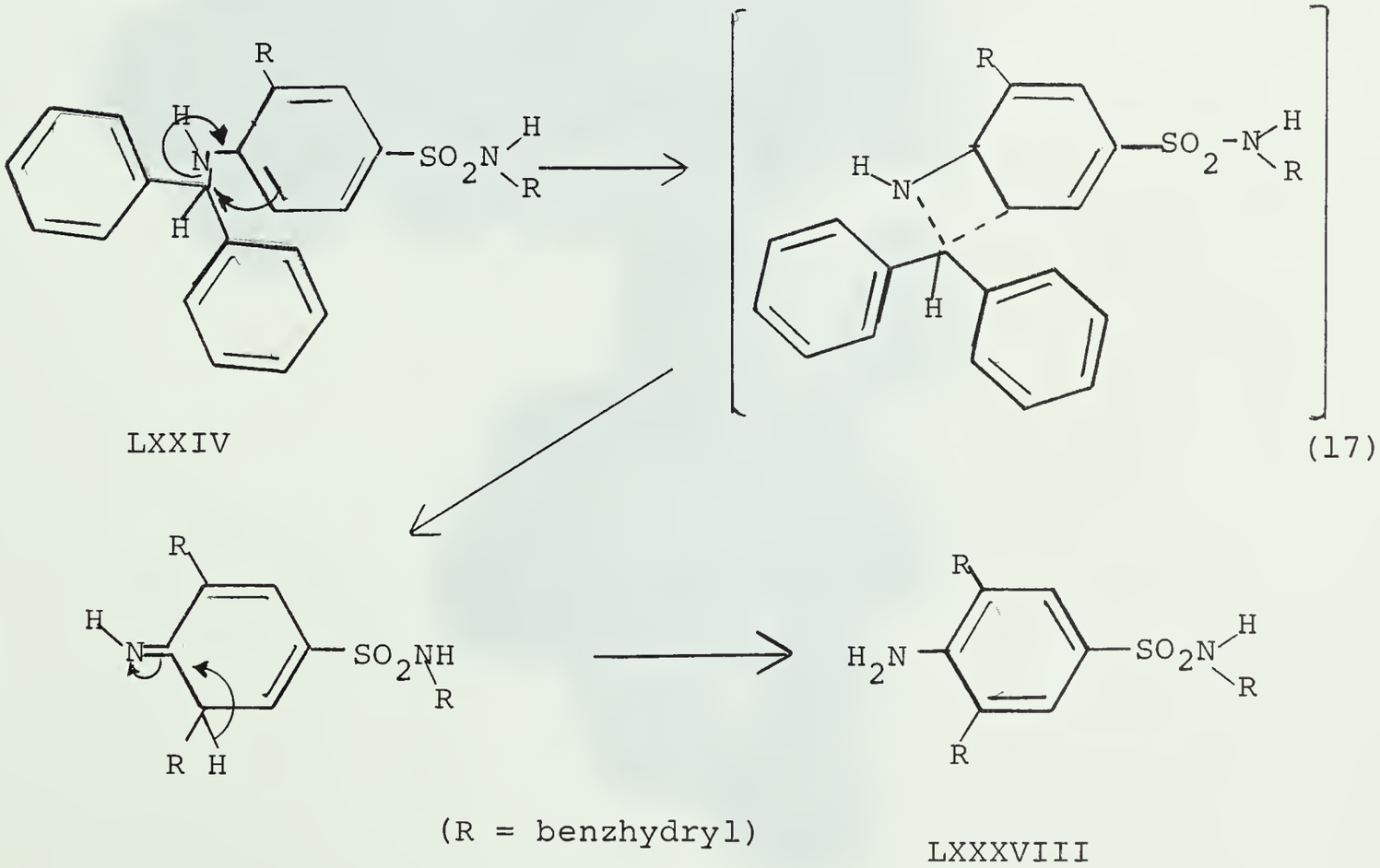


XCII (R = benzhydryl)

of structure LXXIV are present, then from a consideration of relative distance alone, the liberated cation would be expected to be attacked by the reactive site most readily available. This of course would be the ortho position of the molecule that released it. This would seem only logical, since this position is very close to where the ion is liberated. In fact, the N^4-benzhydryl group would be expected to take up a position very close to the ortho position because of the non-bonded interactions with the other adjacent benzhydryl group. This is evident from an examination of a

Fisher-Hirschfelder-Taylor model of the compound (Figure 1). The circled area shows the proximity of this group to the ortho position.

This preferred conformation would result in a minimum amount of non-bonded interaction. At higher temperatures the interactions may increase, which may result in forcing the C-N bond angle to strain significantly, thereby cleaving the bond. If such a strain was occurring, the degree of such a strain may be sufficient to allow a concerted migration to the ortho position. This type of migration could be represented by a mechanism such as shown by equation 17.



LXXIV (17)

(R = benzhydryl)

LXXXVIII

The Fisher-Hirschfelder-Taylor
Model of N^1,N^4,3-Tribenzhydrylsulfanilamide

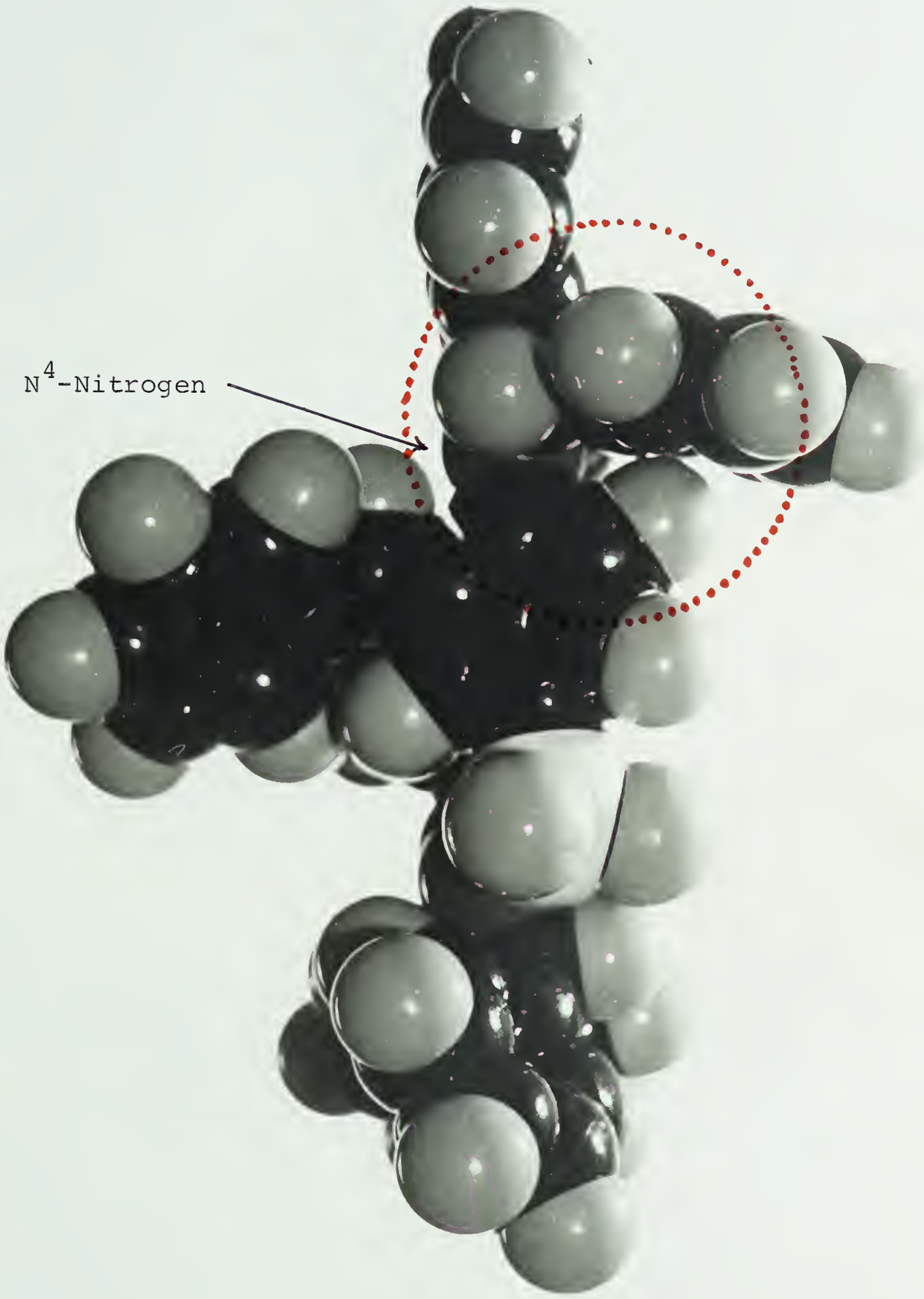
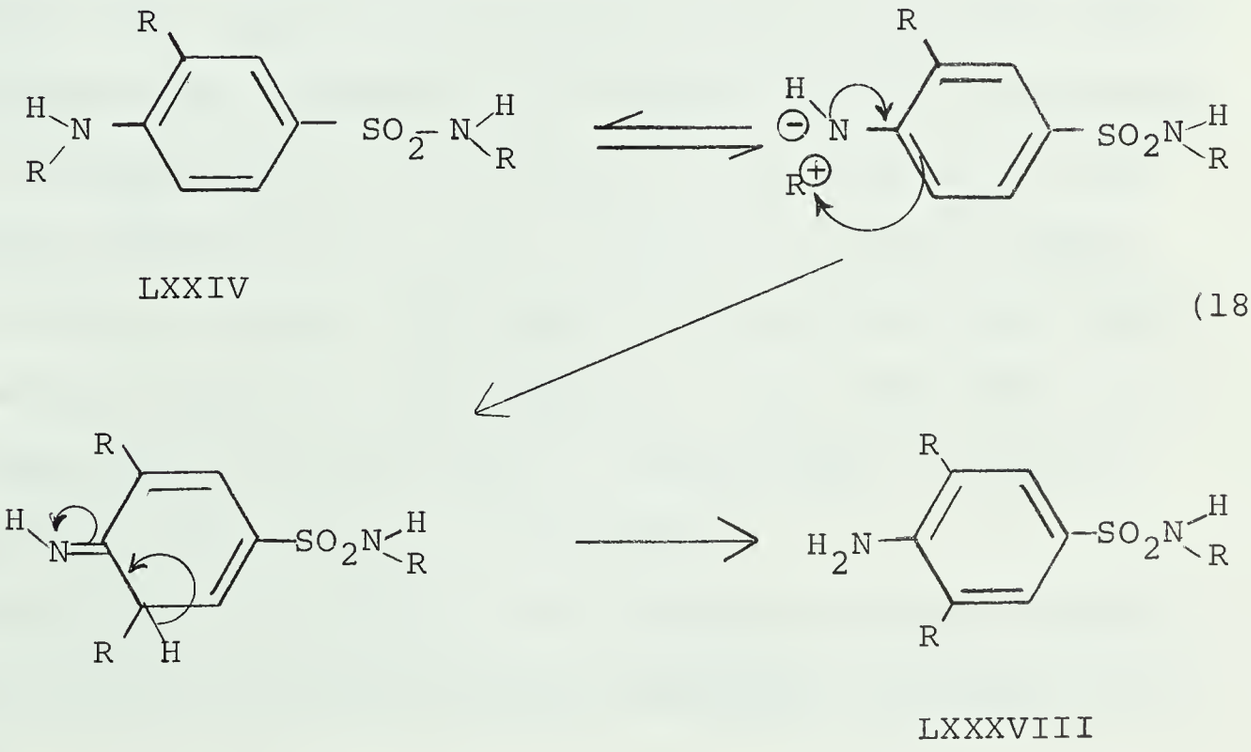


Figure 1

However, the required intermediate constitutes only the equivalent of a four membered ring. In order to get simultaneous bond cleavage and bond formation the relative positions of the two participating bonds must be very close together. Achieving this close proximity with a four membered ring type of intermediate may be difficult because of the bond strain involved.

If, however, the C-N bond cleaved before bond overlap occurred, which may be the more likely situation , the rearrangement could proceed through an ion pair intermediate. The cleaved ion would therefore be held by ionic forces close



LXXIV (18)

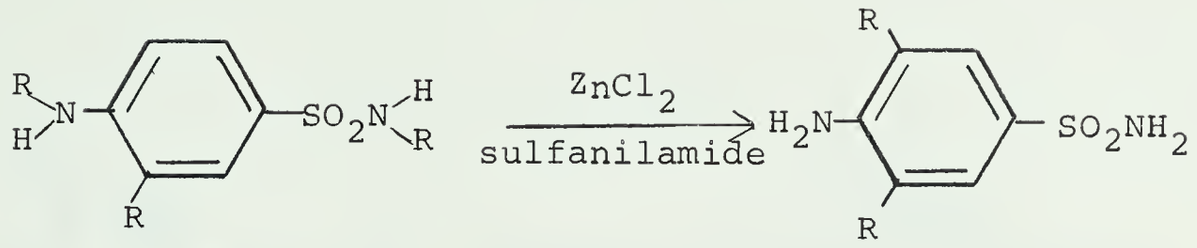
LXXXVIII

(R = benzhydryl)

to the ortho position long enough for a reaction to occur, as illustrated by equation 18. Further work was thus undertaken in an attempt to substantiate the above mechanism. An equimolar ratio of benzhydrol and sulfanilamide, in the presence of zinc chloride, was fused at low temperatures. The product recovered, even though the molar ratio of reactants used was one-to-one, proved to be the trisubstituted compound LXXIV. Since there is evidence that the first step in these fusion reactions is the alkylation of the N^4-nitrogen, it was expected that the N^4-monobenzhydryl derivative would be isolated. The monosubstituted derivative (XC) must therefore be more reactive than the parent sulfanilamide, and the disubstituted derivative (XCI) must be more reactive than either the monosubstituted or the unsubstituted compound towards benzhydrol under the conditions of the reaction. The reasons for the increased reactivities are not apparent, and from a steric point of view at least, this order of reactivity would seemingly be the reverse of that expected, since the ortho positions are hindered by the bulky N^4-substituent. This was evident from their failure to brominate.

When LXXIV was heated in the presence of zinc chloride and pure sulfanilamide, the product isolated was found to be LXXXVI.

Since it has been shown that migration occurred before cleavage of the N^1-substituted benzhydryl group, and since no excess benzhydrol was present in the reaction mixture,



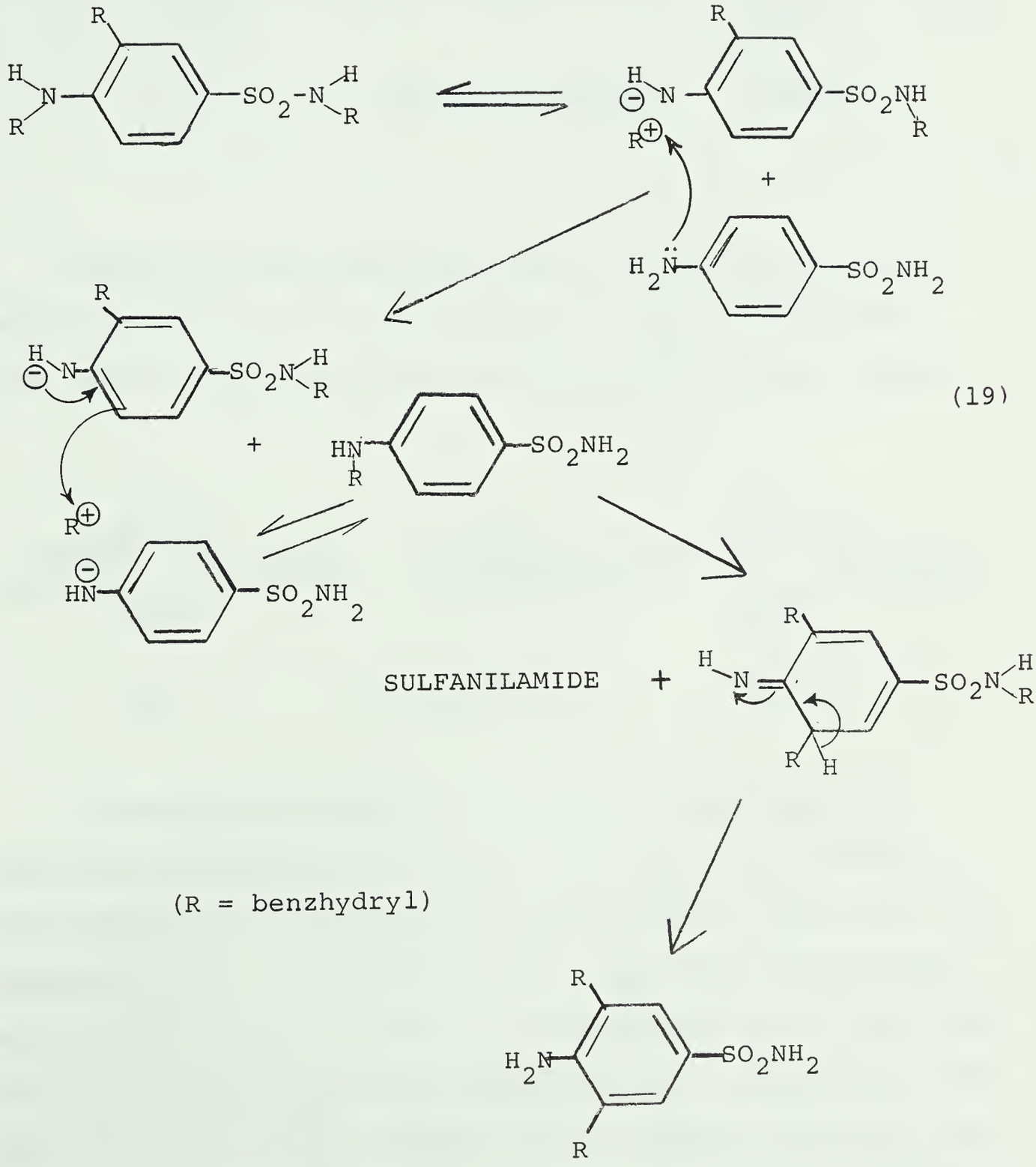
LXXIV (R = benzhydrol) LXXXVI

the latter reaction would provide additional evidence in favour of an intramolecular rearrangement. If the rearrangement had proceeded via an intermolecular process, the free benzhydryl cation should have been incorporated into the unsubstituted sulfanilamide, and various cross products should have been produced. No such products were isolated.

The reaction could, however, have proceeded through an intermolecular transfer mechanism such as that shown by equation 19, and thus avoided the production of any cross products. The liberated benzhydryl groups may have been incorporated into the unsubstituted sulfanilamide, which in turn released the group to another disubstituted molecule, yielding the desired product.

To verify the credibility of such a sequence, the reaction was duplicated, but instead of using sulfanilamide, naphthalene was used as the diluent. The product isolated from the reaction was again found to be LXXXVI.

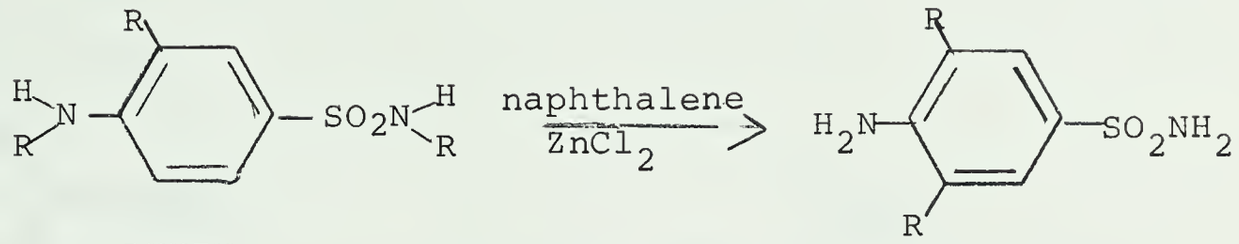
This would tend to rule out the involvement of such a transfer mechanism (equation 19).



SULFANILAMIDE +

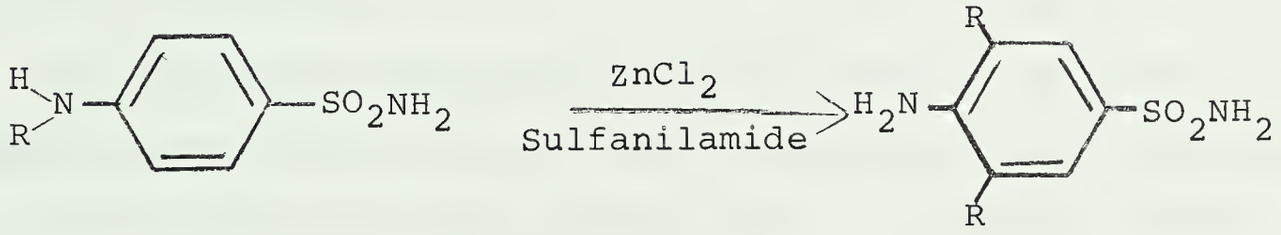
(R = benzhydryl)

(19)



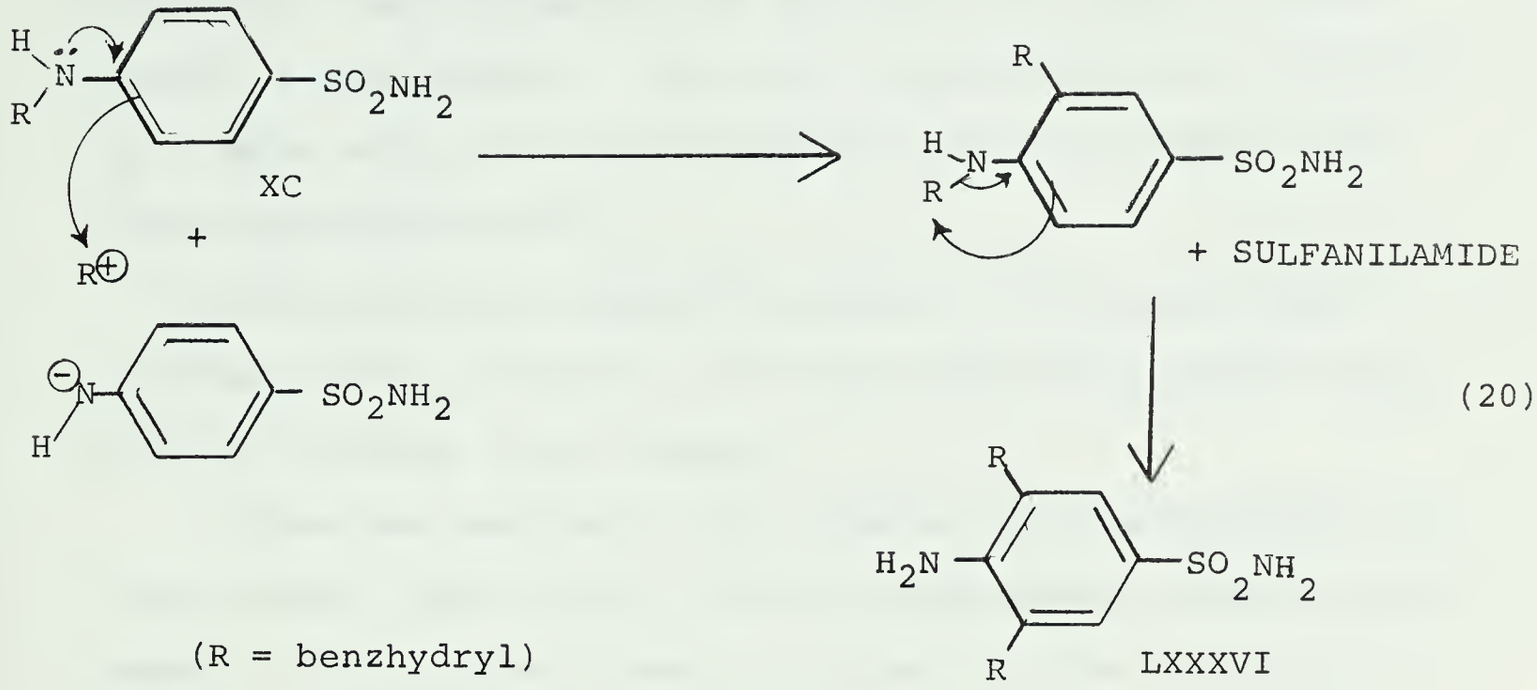
LXXIV (R = benzhydryl) LXXXVI

Reaction of the monosubstituted N^4-benzhydrylsulfanilamide (ref. no. 1), in the presence of zinc chloride and pure sulfanilamide, was also found to yield product LXXXVI.



XC (R = benzhydryl) LXXXVI

Although this reaction was somewhat surprising, it could be explained on the basis of the previous findings on the reactivity of sulfanilamide derivatives. Since only the monosubstituted sulfanilamide (XC), and pure sulfanilamide were present in the reaction, one benzhydryl group must have come from another identical molecule of XC. Presumably, the other benzhydryl group shifted via an internal mechanism, as discussed previously (see equation 17), the product resulting from the sequence of steps illustrated by equation 20.



(20)

(R = benzhydryl)

As one of the molecules of XC is cleaved, the benzhydryl cation which results would be preferentially attacked by another molecule of XC, on the basis of relative reactivities, rather than the same molecule which released the cation. The attack would presumably have been on the ortho position, thus forming the disubstituted derivative which in turn would rearrange to give LXXXVI. Although equation 20 does not show the involvement of the N^1-substitution and cleavage, these steps are more than likely involved in the reaction.

The intermolecular migration of the benzhydryl ion observed in the above reaction would tend to favour the proposal made earlier that the intramolecular migration proceeded via an ion pair mechanism.

When tribenzhydrylsulfanilamide (LXXIV) was heated at 210° with an equal weight of sulfanilamide in the absence of zinc chloride, only starting material was recovered. The benzhydryl rearrangements are therefore not simple thermodynamic rearrangements. The zinc chloride obviously functions as a lewis acid in a manner analagous to that found in the Benzidine Rearrangement.

Rearrangements involving benzhydryl groups have been reported in the literature, but the mechanistic aspects have not been studied in any detail.

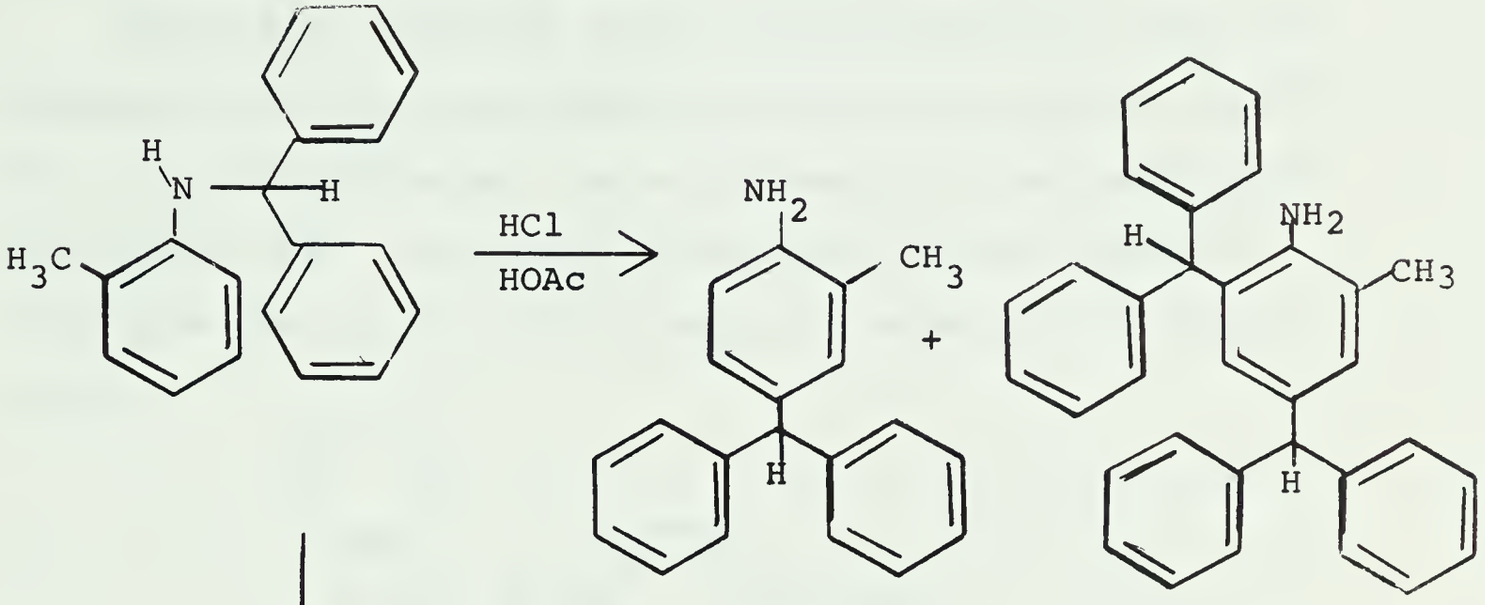
Iddles and coworkers (26) reported the rearrangement of the o-cresol ether, XIII, to the corresponding p-substituted phenol, VIII, in the presence of zinc chloride (equation 4).

Cheeseman and Poller (31) observed the rearrangement of N-benzhydryl salicylamide to the corresponding p-substituted phenol (equation 13). They proposed that the rearrangement involved protonation of the amide-nitrogen atom, heterolysis of the N-alkyl bond, and ring substitution.

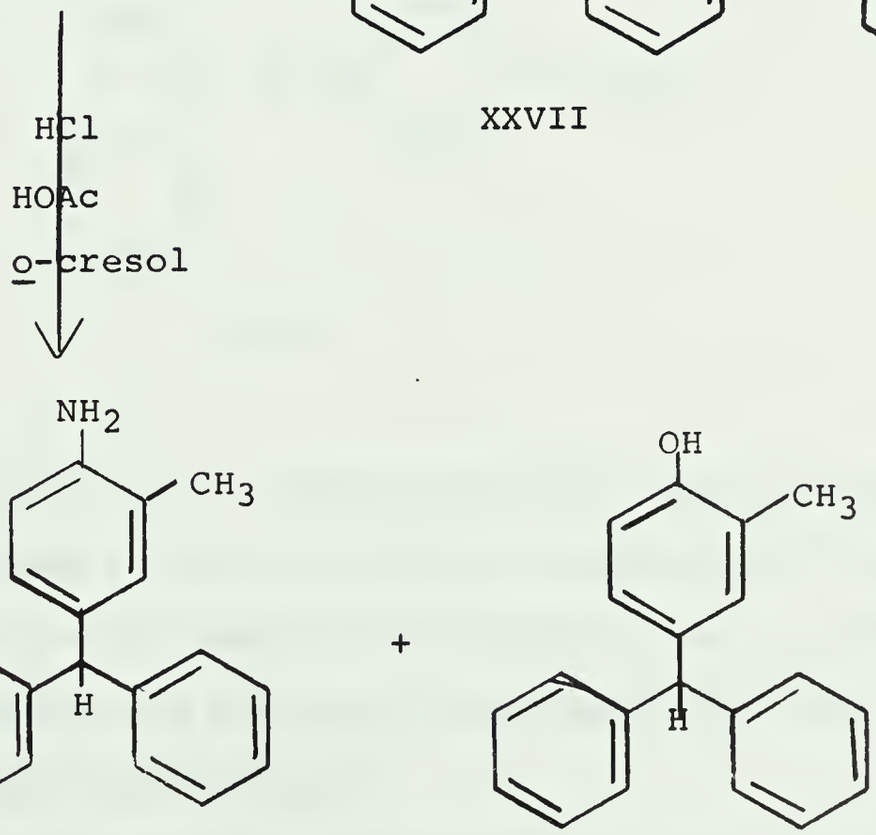
N-Diphenylmethyl-o-toluidine (XCIII) was found to yield two products, namely XXVII and XXVIII, when heated in a hydrochloric-acetic acid medium (27).

They also reacted XCIII with o-cresol, in a hydrochloric-acetic acid medium, and obtained the cross products XXVII and VIII. It was therefore concluded that the rearrangement occurred through an intermolecular process.

The apparent intramolecular rearrangement of the benzhydryl group observed in this study does not appear to have a precedent.



XXVII XXVIII

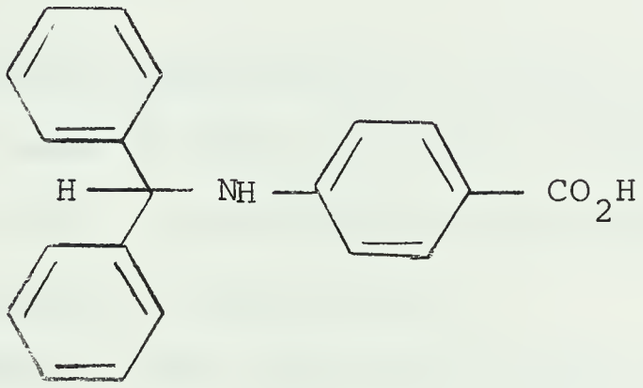


XXVII VIII

Applications of this Reaction

In view of the success of this alkylation reaction with the sulfanilamides, some similar studies were carried out with several related compounds.

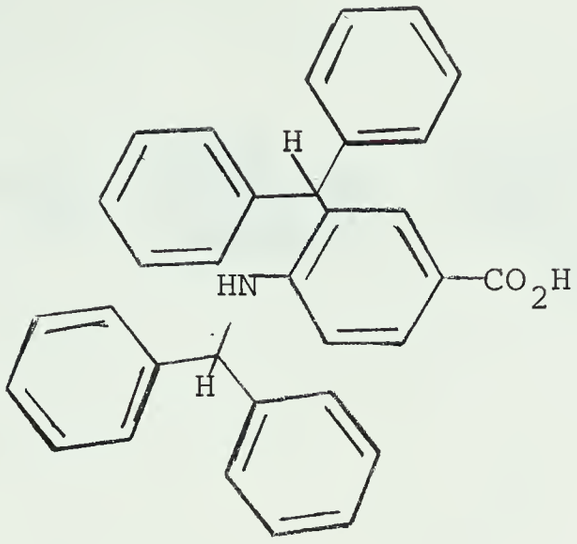
Heating an equimolar ratio of p-aminobenzoic acid and benzhydrol in a nitromethane-perchloric acid medium, at 75° for 20 minutes, yielded the corresponding N^4-monobenzhydryl derivative XCIV. The infrared spectrum of the compound displayed the typical single peak in the amino stretching region.



XCIV

The reaction of a two-to-one molar ratio of benzhydrol to p-aminobenzoic acid, at reflux temperature, for 45 minutes afforded a product shown to be identical with LXXXI. This latter compound was recovered previously from the fusion reaction with sulfacetamide.

The above reaction was repeated, but was stopped after only four minutes of refluxing. Two products were isolated from the reaction mixture; one was the decarboxylated product (LXXXI), the other was found to be the disubstituted compound XCV.

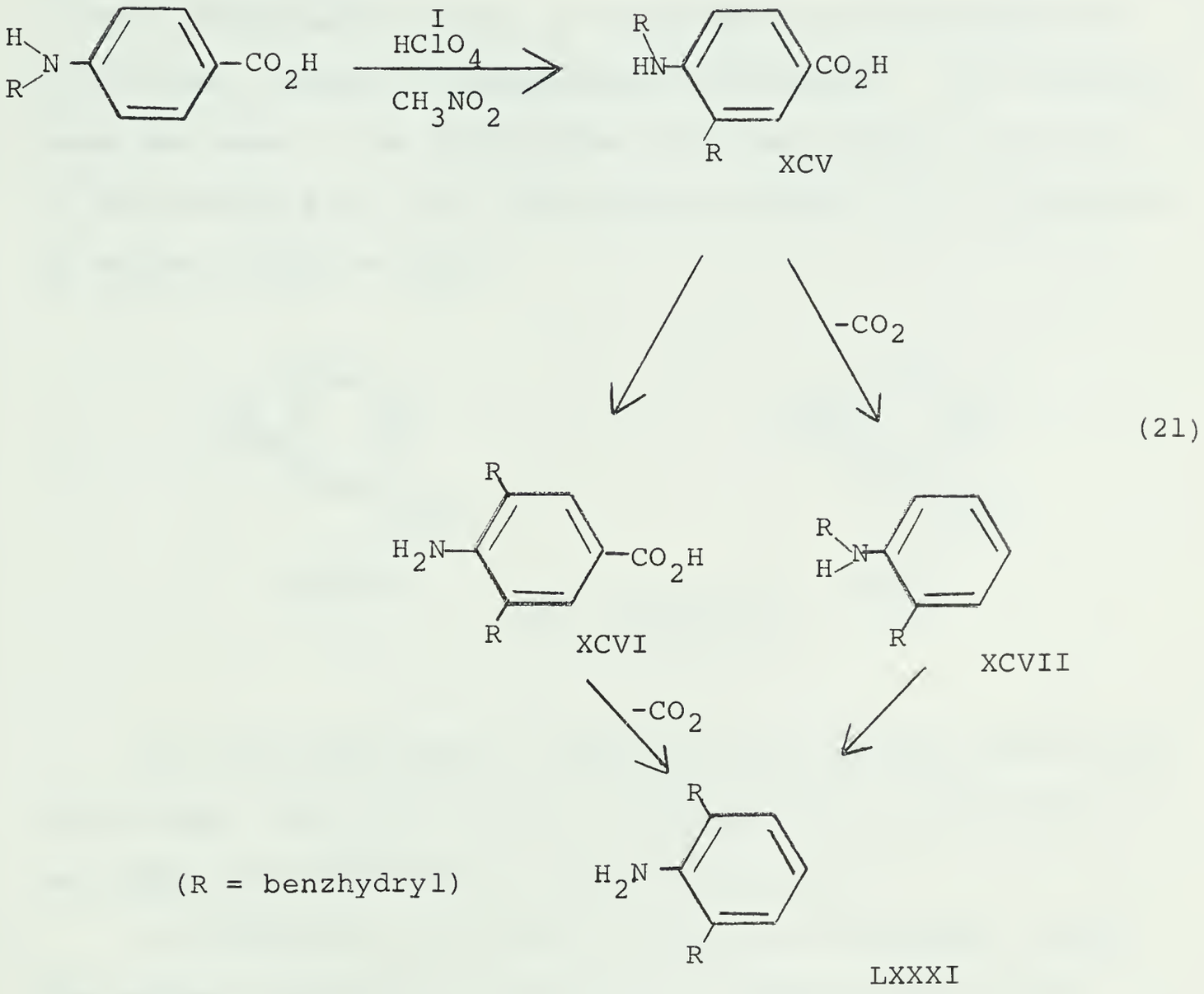


XCV

The infrared spectrum of the latter compound revealed but a single peak at 3333 cm^{-1} and a strong carbonyl absorption at 1665 cm^{-1}. This result would suggest a sequence of steps illustrated by equation 21.

Furthermore, this observation would tend to support the rearrangement sequence discussed earlier for the reaction with sulfanilamide (equation 15). Finally, it would appear to negate the possibility of the compound LXXXI being the 2,4-dibenzhydryl derivative, since substitution of both benzhydryl radicals must precede decarboxylation.

An attempt was made to determine whether the rearrangement of XCV to LXXXI actually preceded or followed decarboxylation. However, on fusing p-aminobenzoic acid with benzhydrol, in the presence of zinc chloride at 150° for 45 minutes, only compound LXXXI was recovered and neither of the expected intermediates XCVI or XCVII could be isolated.



XCV

XCVI

XCVII

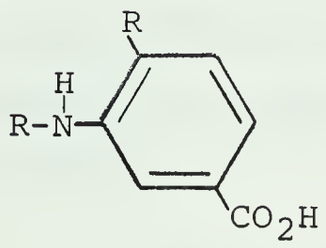
LXXXI

(21)

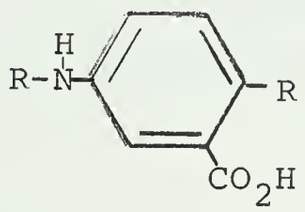
It is interesting to note that aside from p-aminobenzoic acid, the only sulfanilamide which cleaved at fusion temperature to yield the disubstituted aniline (LXXXI) was the N^1-acetyl derivative (sulfacetamide). Neither sulfanilamide itself, nor any of the other N^1-monosubstituted sulfanilamides studied showed this behavior. The unique role of the acetyl group in facilitating the cleavage of the sulfonamido group is

not immediately apparent.

The reaction of a two-to-one molar ratio of benzhydrol to meta aminobenzoic acid, by refluxing in nitromethane for 45 minutes, yielded a disubstituted derivative. The nitrogen atom was shown to be substituted from the infrared features of the molecule and thus the product must be that illustrated by either XCVIII or XCIX.



XCVIII



XCIX

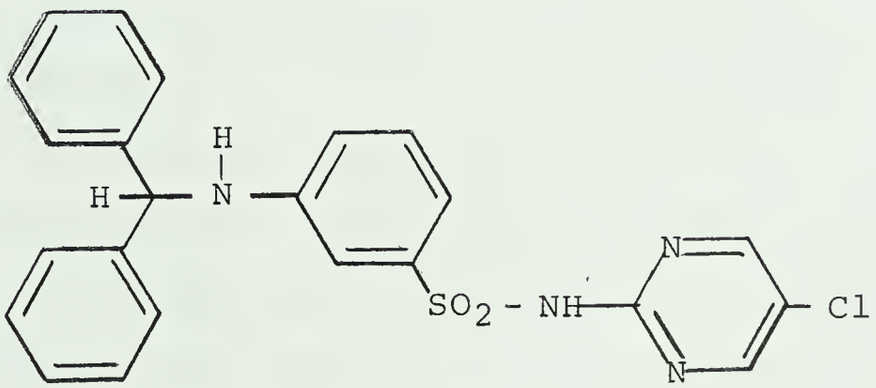
(R = benzhydryl)

As one would expect, decarboxylation did not occur with this isomer since the driving influence of the amino group is no longer operative when in the meta position.

If XCVIII was the correct structural assignment, under the higher temperature conditions of fusion, the di-ortho substituted product should be obtained, whereas if XCIX were the product, then the identical compound would be expected from the fusion reaction. Unfortunately, when carried out, a gummy material was obtained which could not be crystallized. By analogy with some of the previously isolated products, the structure XCVIII would have to be favored for this product, however, the other structure remains a possibility and further

work would be required before a positive structural assignment could be made.

The reaction of the N^1-monosubstituted metanilamide, metachloridine, with an equimolar ratio of benzhydrol in nitromethane, afforded the corresponding N^3-monobenzhydryl derivative (C). Employing a two-to-one molar ratio of benzhydrol to metachloridine under the same reaction conditions yielded a dibenzhydryl derivative. The compound was titratable, and on the basis of its infrared spectrum, was also substituted at the N^3 position.

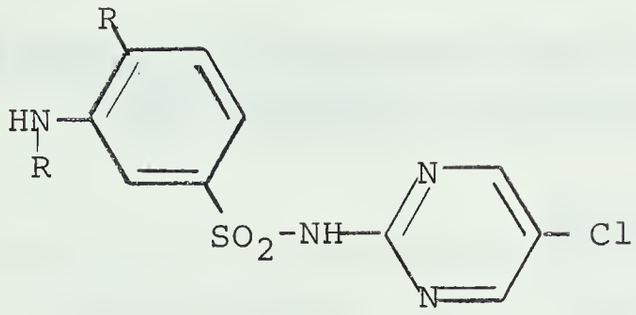


C

As was true of meta aminobenzoic acid, assignment of the second site of substitution is difficult. However, on examination of molecular models of the possibilities, the para position was considerably more sterically hindered by the rather large SO_2 group than was the ortho position. Accordingly, this compound is most likely that given by structure CI.

The results of this study suggest the applicability of benzhydrol as a reagent for a wide variety of ring-substituted

primary aromatic amines.



CI (R = benzhydryl)

Practical Applications of this Reaction

Although Moskalyk and Chatten (1) were able to recover xanthenyl derivatives for all the sulfanilamides which they studied, they felt that the derivatives were of relatively limited practical value for their identification and differentiation due to the inherent instability of the compounds.

Examination of the melting points of the benzhydryl-sulfanilamides prepared in this study, coupled with the fact that these derivatives are stable and easily purified, revealed that these compounds could be usefully employed for the above mentioned purpose.

It may be seen from Table VI that the benzhydryl derivatives melt in the range of approximately 150°-250°. This is generally considered to be the useful melting point range for derivatives. In addition, the melting points of the derivatives are, in general, quite widely spaced. Although several derivatives melt at nearly identical temperatures, the melting

TABLE VI

Melting Points of N^1-Monosubstituted Sulfanilamides and their Benzhydryl Derivatives

Ref. No.	Sulfanilamide	Melting Point °C	
		Parent	Benzhydryl Derivative
1	Sulfanilamide	164.5-165.5	175-176
1t	Sulfanilamide	164.5-165.5	206-208
1bx	Sulfanilamide	164.5-165.5	245-245.5[a,b,c]
2	Sulfadiazine	252-256	253-255[d]
3	Sulfapyridine	250	212-214[e]
4	Sulfamerazine	238	213.5-215
5	Sulfamethazine	176	200.5-202
6	Sulfamethizole	208	212-212.5
6d	Sulfamethizole	208	202-204
6bx	Sulfamethizole	208	253-254
7	Sulfachloropyridazine	197	225-226
7bx	Sulfachloropyridazine	197	216-218
8	Sulfamethoxypyridazine	186-187	206-208
8bx	Sulfamethoxypyridazine	186-187	223.5-224
9	Sulfacetamide	216	208-208.5
10	Sulfaguanidine	190-193	244-246
11	Sulfaphenazole	179-183	238-239
12	Sulfaquinoxaline	247-248	224-225

continued

TABLE VI (continued)

13	Sulfanilanilide	193	153-154
13d	Sulfanilanilide	193	236-238
13d'	Sulfanilanilide	193	216-218
14	Sulfamethoxazole	169-172	209-209.5
15	Sulfadimethoxine	220-223	175-176
15t	Sulfadimethoxine	220-223	177-179
15bx	Sulfadimethoxine	220-223	174-177
16	Sulfaproxyline	192-193	200.5-201.5
17	Sulfisoxazole	194	188-188.5
17d	Sulfisoxazole	194	210-211
17bx	Sulfisoxazole	194	184-185
18	Sulfathiazole	204-205	229.5-230.5
18bx	Sulfathiazole	204-205	211.5-212
19	Sulfaethylthiadiazole	185.5-186	197
19d	Sulfaethylthiadiazole	185.5-186	207.5-208.5
19bx	Sulfaethylthiadiazole	185.5-186	204-205.5

In addition to those derivatives listed in the Table, the following derivatives were also obtained:

a - N^1,3,5-Tribenzhydrylsulfanilamide (193-194.5°)
b - N^1-Xanthenyl-3,5-dibenzhydrylsulfanilamide (207-208°)
c - 3,5-Dibenzhydrylsulfanilamide (296°)
d - N^1-(2-Pyrimidyl)-N^4,3-dibenzhydrylsulfanilamide (249-250°)
e - N^1-(2-Pyridyl)-N^4,3-dibenzhydrylsulfanilamide (232.5-234.5°)

points of the parent sulfanilamides differ significantly so that they may easily be distinguished. For example, the N^4-benzhydryl derivatives of sulfaquinoxaline and sulfachloropyridazine melt at 224°-225° and 225°-226°, however, the parent sulfanilamides melt at 247°-248° and 197°, respectively. Thus, these derivatives provide a useful means for the ready identification and differentiation of sulfanilamides.

Antibacterial Evaluation

The derivatives prepared in this study were tested for inhibitory action on microorganisms. Since only a preliminary indication was desired, the standard cup plate and filter paper disc methods were not employed. The method used consisted of placing several milligrams of the solid sample onto a plate containing solid Mueller Hinton medium inoculated with E. coli or S. aureus. The plates were incubated at 37°C, and periodic examinations were made to determine if growth was inhibited in the zone surrounding the test sample.

All but two of the derivatives showed no apparent zone inhibitions. The derivative of sulfaethylthiadiazole (ref. no. 19) exhibited significant growth inhibition. However, it was found that certain samples of this product showed no activity, and therefore more work would be required before the nature of the compound which exhibited the inhibitory activity could be revealed.

The N-monobenzhydryl derivative of p-aminobenzoic acid (XCIV) was less active, but nevertheless, did show some activity. Once again, no further work was undertaken with this compound at this time, but further studies with compounds related to those displaying activity would appear to be warranted.

Summary

The major points embodied in this research project may be represented as follows:

(a) Benzhydrol, when condensed with N^1-monosubstituted sulfanilamides in a nitromethane solvent employing a strong acid catalyst, under varied reaction conditions, yielded monosubstituted derivatives in all cases. However, with several sulfanilamides, dibenzhydryl derivatives were isolated when a two molar ratio of the alcohol was employed. Sulfanilamide itself, and sulfadimethoxine under the latter reaction conditions, afforded trisubstituted derivatives.

(b) The site of the substitution of the benzhydryl radical common to all the sulfanilamides having a free para amino group, was shown to be the N^4- position in the sulfanilamide molecule. The one exception was the dibenzhydryl derivative of sulfanilanilide (compound no. 13d).

(c) The site of substitution of the second benzhydryl moiety, in the dibenzhydryl derivatives, was shown to be one of the following positions:

(i) on the annular nitrogen atom, as a result of condensation with the imido tautomeric form of the sulfanilamide (compounds 6d and 19d).

(ii) on the extra ring nitrogen atom at the N^1-position, reaction having occurred from the amido tautomeric form (compound 17d).

(iii) on the para position of the N^1-phenyl group (compound 13d').

(d) As opposed to the xanthenyl derivatives (1), the benzhydryl derivatives of the sulfanilamides proved to be stable and easily purified compounds, regardless of the site or sites of substitution.

(e) The N^4-monobenzhydrylsulfanilamides of those sulfanilamides which yielded dixanthenyl derivatives, when reacted with xanthydrol, afforded in each instance the corresponding monobenzhydryl-monoxanthenyl derivatives. The sites for the condensation of the 9-xanthenyl radical were found to be the same positions as those in the dixanthenyl derivatives (1). These benzhydryl-xanthenyl derivatives were found to be stable and easily purified compounds, further supporting the findings of Moskalyk and Chatten (1), that the instability of the dixanthenylsulfanilamides was due to the weak nature of the $C-N^4$ bond.

(f) The fusion of p-toluidine with benzhydrol in the presence of zinc chloride was shown to yield a different product than that reported by Giraud (44). He reported that the derivative was the N,N-bisdiphenylmethyl compound. However, this study has shown the compound to be 2,6-dibenzhydryl-4-methyl aniline.

(g) By applying this latter reaction to sulfanilamides, a variety of substitution products were recovered with a number of sulfanilamides. The majority of the derivatives were found to be disubstituted; reaction having occurred at one of the following positions:

(i) on the N^4-nitrogen atom and the position ortho to this nitrogen atom.

(ii) on the two positions ortho to the N^4-nitrogen atom.

(h) Three sulfanilamides yielded N^4-monosubstituted derivatives when fused, however, these condensations were performed under much milder reaction conditions.

(i) The fusion of sulfanilamide with benzhydrol, in the presence of zinc chloride at various reaction temperatures, was found to yield a variety of derivatives. A sequence of steps leading to each of these products, one of which involves an intramolecular rearrangement of a benzhydryl moiety from the N^4-position to the adjacent ortho position, were shown to be involved.

(j) The benzhydrylsulfanilamides were tested for and found, in general, to be devoid of any antibacterial activity.

(k) In view of the relative ease of preparation and purification of the benzhydryl derivatives, and because of the favorable melting point distribution of these compounds, they would appear to be most suitable for use in the identification and differentiation of the bacteriostatic sulfanilamides.

EXPERIMENTAL

All melting points recorded in this investigation were taken on a Thomas-Hoover capillary melting apparatus and are uncorrected.

Infrared spectra were recorded on a Perkin-Elmer infrared spectrometer, model 21. Nuclear magnetic resonance spectra were recorded on a Varian Associates Model A-60 spectrometer.

Elemental analyses were performed by Messrs. Weiler and Strauss and by the Department of Chemistry, Microanalysis Laboratory, University of Alberta.

Experiments Related to the Preparation of Benzhydryl Derivatives of Sulfanilamides

Benzhydrol was obtained as the commercial product from Eastman Kodak Co. Inc., New York.

The Sulfanilamides were either obtained commercially or were generous gifts of the manufacturers.

Experiments Leading to the Adoption of a Generally Applicable Procedure

A. Equimolar amounts (0.006 mole) of sulfanilamide, toluene-p-sulfonic acid and benzhydrol were dissolved in 10 ml. of glacial acetic acid. The solution was refluxed for 45 minutes and then poured into 100 ml. of water. A viscous gum separated and repeated attempts at solidifying the material failed.

The condensation of sulfacetamide, sulfamethazine, sulfamerazine, and sulfamethoxypyridazine under identical reaction conditions also produced unresolvable gums.

B. Equimolar amounts of benzhydrol and toluene-p-sulfonic acid (0.006 mole) were dissolved in 10 ml. of glacial acetic acid and the solution heated to reflux. Sulfanilamide (0.006 mole), dissolved in a minimum amount of dimethylformamide (DMF), was slowly dripped into the solution and the reaction mixture was then refluxed for a further 45 minutes. On pouring the solution into water, a white precipitate appeared to be formed, however, on attempted isolation of the precipitate it again turned into a viscous gum. Repeated attempts at crystallizing this material failed.

The reaction was repeated at room temperature, but only the starting sulfanilamide was recovered.

C. A solution of 1.0 g. (0.004 mole) sulfadiazine, 0.73 g. (0.004 mole) of benzhydrol and three drops of concentrated sulfuric acid, in 10 ml. of glacial acetic acid, was refluxed for 30 minutes. Upon adding the solution to water, an orange precipitate separated. After many recrytallizations from ethanol, the product exhibited a constant melting point of 240.5-242°. No attempts were made at elucidating the structure of this compound.

Treatment of sulfamerazine under the same reaction conditions led to an unresolvable gum. On extending the reaction time to 90 minutes, a small amount of white product which did

not melt below 300° was isolated. No attempt was made at determining the identity of this material.

D. A solution of 1.0 g. (0.0036 mole) of sulfamethoxypyridazine with an equimolar ratio of benzhydrol and 10 drops of concentrated sulfuric acid, in 10 ml. of glacial acetic acid, was refluxed for 30 minutes and then poured into water. Once again a compound which did not melt below 300° was isolated, and no attempt was made at elucidating its structure.

General Procedure for the Preparation of the Benzhydryl-sulfanilamides

One gram of the sulfanilamide and an equimolar ratio of benzhydrol were dissolved in a minimum amount of boiling nitromethane. Approximately five drops of 70% perchloric acid were added and the solution was refluxed for 45 minutes, while being stirred electromagnetically. The reaction was discontinued if a precipitate developed prior to the stated time. Cooling to room temperature or in ice normally resulted in precipitation of the product. However, if cooling did not yield a product, the solution was concentrated in vacuo. If a viscous gum formed upon concentration of the reaction mixture, it was crystallized by stirring with cold ethanol. The crude material was washed with cold nitromethane and dried. With some of the sulfanilamides, lower temperatures and varying reaction times were necessary to obtain the product. Also, in some cases hydrochloric acid proved more effective than perchloric acid as the catalyst.

The specific conditions employed to obtain the benzhydrylsulfanilamides listed in Table I are shown in Table VII.

Xanthenyl Derivatives of Monobenzhydrylsulfanilamides

These were prepared by the method reported by Moskalyk and Chatten (1). To 1 g. (0.005 mole) of xanthydrol in 15 ml. of glacial acetic acid was added an equimolar amount of the sulfanilamide derivative dissolved in a minimum volume (2-5 ml.) of N,N-dimethylformamide (DMF) while stirring electromagnetically. Stirring was continued for a period of 15-30 minutes beyond the time the derivative first began separating. The product was collected on a medium porosity sintered glass funnel, washed well with cold ethanol and dried in a vacuum desiccator over P_2O_5. The data for these compounds are contained in Table II.

Experiments Related to the Structural Elucidation of the Mono, Di, and Tribenzhydryl Derivatives

Furfural as a Reagent for the Detection of Primary Aromatic Amines

The color test was performed as described by Hucknall and Turfitt (53) and Moskalyk and Chatten (1). To 0.1 mg. to 1 mg. of the derivative contained in a porcelain spot plate was added 1 drop of a 2% solution of furfural in glacial acetic acid. The liquid was allowed to evaporate and the color produced was noted and compared with that from the parent compound. The parent compounds each afforded a violet color whereas each of

TABLE VII

Experimental Details Employed to Obtain the Benzhydrylsulfanilamides Listed in Table I, Employing the General Method

Ref. No.	Sulfanilamide [a]	ml. of nitromethane	Drops of Perchloric Acid	Temp. of Heating °C	Time kept at this Temp. (Min.)
1	Sulfanilamide	10	3	65	40
1t	Sulfanilamide	7	5	75	20
2	Sulfadiazine	10	6	reflux	10
		10	3	75	10
3	Sulfapyridine	10	6	reflux	45
		10	3	80	20
4	Sulfamerazine	10	10	reflux	45
		10	5	80	20
5	Sulfamethazine	10	5	reflux	45
6	Sulfamethizole	10	10	reflux	45
		7	5	80	20
6d	Sulfamethizole [b]	15	5	80	10
7	Sulfachloropyridazine	10	5	reflux	45
		7	5	80	20
8	Sulfamethoxypyridazine	10	5	reflux	45
		10	5	80	25
9	Sulfacetamide	10	5	reflux	45
10	Sulfaguanidine	10	10	reflux	45

continued

TABLE VII (continued)

11	Sulfaphenazole	10	10	reflux	45
12	Sulfaquinoxaline	10	10	reflux	45
13	Sulfanilanilide	5	8[c]	reflux	45
13d	Sulfanilanilide[b]	5	3	reflux	45
13d'	Sulfanilanilide[b]	5	5	80	35
14	Sulfamethoxazole	10	3	68	3
15	Sulfadimethoxine	10	3	70	10
		8	8	reflux	45
15t	Sulfadimethoxine[b]	10	7	85	30
16	Sulfaproxyline	10	5	75	10
17	Sulfisoxazole	10	5	reflux	45
		8	8[c]	reflux	45
17d	Sulfisoxazole[b]	10	5	reflux	45
		10	5	80	10
18	Sulfathiazole	10	5	reflux	45
		10	3	75	10
19	Sulfaethylthiadiazole	7	5	reflux	45
		7[d]	5	80	20
		15[c]	15	reflux	45
19d	Sulfaethylthiadiazole[b]	10	5	reflux	45

a - 1.0 g of each of the sulfanilamides listed was reacted with a molar ratio of benzhydrol.
b - 1.0 g of the sulfanilamide was reacted with a two molar ratio of benzhydrol.
c - refers to hydrochloric acid rather than perchloric acid
d - refers to dioxane rather than nitromethane

the benzhydryl derivatives remained colorless.

Nonaqueous Titration of the Derivatives as Acids

Employing chloroform as the solvent and phenolphthalein as the indicator, the benzhydrylsulfanilamides were titrated with a 0.1 N solution of potassium hydroxide in methanol. The results are presented in Table III.

N-Phenyl-p-Toluenesulfonamide was prepared by the standard Schotten-Baumann reaction.

To 0.3 ml. of aniline in a test tube was added 5 ml. of 10% sodium hydroxide solution and 0.4 ml. of p-toluenesulfonyl chloride. The solution was stoppered and shaken vigorously. On completion of the reaction the solution was acidified and a precipitate resulted. Recrystallization from ethanol yielded the title compound melting at 100.5-102.5°. Lit. m.p. 103° (70).

N-(p-Benzhydrylphenyl)-p-toluenesulfonamide was isolated by treating 2 g. (0.004 mole) of N-phenyl-p-toluenesulfonamide with an equimolar amount of benzhydrol and 15 drops of 70% perchloric acid in a minimum amount of nitromethane for 25 minutes. The reaction mixture became very dark reddish-black after this period of time. The reaction mixture was concentrated in vacuo and the product isolated was in the form of a gum. Stirring the gum with 10% sodium hydroxide yielded a solid precipitate which did not melt below 300°. Acidification of an ethanolic solution of the product afforded the title compound, which after several recrystallizations from ethanol and water, melted at 176.5°-177°.

Calc. for $C_{26}H_{23}NO_2S$: C, 75.51; H, 5.60; N, 3.39.

Found: C, 75.30; H, 5.39; N, 3.30.

A single peak at 3250 cm^{-1} was displayed in the infrared spectrum. The SO_2 symmetric stretching vibration appeared at 1160 cm^{-1}. The title compound was also prepared by heating 2 g. (0.004 mole) of N-phenyl-p-toluenesulfonamide with an equimolar ratio of benzhydrol in a minimum amount of nitromethane and 10 drops of perchloric acid at 80° for 35 minutes. Cooling afforded a precipitate which after three recrystallizations from ethanol and water melted at 176.5-177°. A mixed melting point determination with the compound above failed to show any depression.

N¹-(p-Benzhydrylphenyl)-3-benzhydryl-5-bromosulfanilamide was prepared by the bromination method described by Moskalyk and Chatten (1). To 1.0 g of N¹-(benzhydrylphenyl)-3-benzhydrylsulfanilamide (compound no. 13d) in a minimum amount of acetone, brominating solution (15 g. of KBr and 10 g. of bromine in 100 ml. of water) was added dropwise with constant stirring. The yellow color continued to disappear until finally a white product separated. Addition of the brominating solution was continued until no more product formed. A 50 ml. portion of water was added, the product was filtered and washed with a dilute solution of sodium bisulfite, followed by water. Two recrystallizations from ethanol yielded a white product melting at 224.5°-225.5°.

Calc. for $C_{38}H_{31}BrN_2O_2S$: C, 69.20; H, 4.75; N, 4.25.

Found: C, 69.35; H, 4.79; N, 4.07.

Similar treatment of N^1-(p-benzhydrylphenyl)-N^4-benzhydrylsulfanilamide (compound no. 13d') revealed that the compound would not take up any bromine.

Attempted Acid Hydrolysis of N^1-(p-benzhydrylphenyl)-N^4-benzhydrylsulfanilamide (compound no. 13d').

The hydrolysis was performed by a method similar to that reported by Snyder and Heckert (71). To 40 ml. of 48% hydrobromic acid was added 4 g. of the benzhydryl derivative. Heating to reflux temperature failed to dissolve the derivative, so 10 g. of phenol was added to increase the solubility. The derivative dissolved, but an oily layer separated on the surface. Refluxing for 45 minutes turned the oily layer a red color. The solution was extracted with ether, and a very small amount of gum was isolated; attempted purification, however, failed. The acidic solution was then basified with sodium hydroxide and extracted with both chloroform and ether. Again only a small amount of gum was isolated which again could not be crystallized. Bringing the solution to a neutral pH, and again extracting with the latter solvents, failed to yield any products. Concentration of the reaction mixture gave a viscous gum, but all attempts at solidification failed.

Hydrolysis of N^1, N^4,3-Tribenzhydrylsulfanilamide (compound no. 1t) was again performed by a method similar to that used by Snyder and Heckert (71). A solution of 4.3 g. of the

derivative and 10 g. of phenol in 50 ml. of 48% hydrobromic acid was refluxed for three hours. At the end of this time an orange oil had separated, which disappeared when the solution was neutralized. Extraction with ether and chloroform yielded a very small quantity of a yellow oil, however, during the extraction process a solid material separated at the interface of the two immiscible solvents. This material, which melted at 247-248.5° (ethanol-water), was shown to be 3-benzhydrylsulfanilamide.

Calc. for $C_{19}H_{18}N_2O_2S$: C, 67.43; H, 5.36; N, 8.28.
Found: C, 67.03; H, 5.51; N, 8.36.

The infrared spectrum displayed peaks at 3413, 3333, 3279 and 3185 cm^{-1}.

3-Benzhydryl-5-bromosulfanilamide. The procedure followed for this reaction was the same as that given earlier for the bromination of the sulfanilanilide derivative (compound 13d). However, even after excess bromine was added, the derivative failed to precipitate from the solution. Concentration of the solvent provided the title compound, which when recrystallized three times from an ethanol and water mixture melted at 153-155.5°.

Calc. for $C_{19}H_{17}BrN_2O_2S$: C, 55.94; H, 3.99; N, 6.53
Found: C, 55.72; H, 4.26; N, 6.24

The infrared spectrum displayed three peaks at 3356, 3247 and 3175 cm^{-1}.

Attempted Bromination of N^1,N^4, 3-Tribenzhydrylsulfanilamide (compound no. 1t).

The bromination was attempted according to the procedure mentioned earlier for the bromination of the sulfanilanilide derivative (compound no. 13d). The compound failed to take up bromine and only the starting material was isolated from the reaction mixture.

Reaction Products by Fusion of Sulfanilamides with Benzhydrol in the Presence of Zinc Chloride

2,6-Dibenzhydryl-4-Methylaniline was prepared following the method reported by Giraud (44). To 2 g. (0.019 mole) of the amine and 3.5 g. (.038 mole) of benzhydrol was added 1 g. of zinc chloride. The reaction mixture was heated in an open tube in a glycerine bath for two hours at approximately 150°. After cooling, the solid residue was stirred with ethanol. The addition of the ethanol provoked the immediate formation of fine crystals which melted at 188° after several crystallizations from ethanol. Lit. m.p. 188° (44).

Calc. for $C_{33}H_{29}N$: C, 90.16; H, 6.65; N, 3.19.

Found: C, 90.14; H, 6.54; N, 3.42.

The infrared spectrum displayed two peaks at 3390 and 3322 cm^{-1}.

2,6-Dibenzhydrylaniline was recovered from the fusion of sulfacetamide with benzhydrol by the aforementioned procedure employed with p-toluidine. The title compound was isolated from the reaction mixture after stirring with alcohol. After

several recrystallizations from an acetone-water mixture, the product melted at 174°-175.5°.

Calc. for $C_{32}H_{27}N$: C, 90.31, H, 6.35; N, 3.29.

Found: C, 90.63; H, 6.04; N, 3.29.

The infrared spectrum displayed two peaks at 3425 and 3356 cm^{-1}. No carbonyl absorption was present.

N^1-(2-Pyridyl)-N^4,3-Dibenzhydrylsulfanilamide. This compound was obtained by fusing 1.0 g. (0.004 mole) of sulfapyridine with 1.47 g. (0.008 mole) of benzhydrol in the presence of 1.1 g. (0.008 mole) of zinc chloride at 150° for 10 minutes.

The same product was also obtained from a similar reaction mixture fused for 45 minutes at 185°. Stirring with ethanol afforded a white product which, after three crystallizations from ethanol melted at 232.5°-234.5°.

Calc. for $C_{37}H_{31}N_3O_2S$: C, 76.39; H, 5.37; N, 7.22.

Found: C, 76.26; H, 5.43; N, 7.07.

The infrared spectrum displayed an amino stretching vibration at 3390 cm^{-1}. The SO_2 symmetric stretching vibration appeared at 1147 cm^{-1}.

N^1-(2-Pyridyl)-3,5-dibromosulfanilamide was prepared by the bromination of sulfapyridine employing the method described earlier for the bromination of the sulfanilanilide derivative (compound no. 13d). After two recrystallizations from ethanol, the compound melted at 253-255°. Lit. m.p. 251° (75).

Attempted Condensation of N^1-(2-Pyridyl)-3,5-dibromosulfanilamide with benzhydrol. Fusion of 2.0 g. (0.005 mole) of

N^1-(2-pyridyl)-3,5-dibromosulfanilamide with an equimolar ratio of benzhydrol in the presence of 1.8 g. (0.01 mole) of zinc chloride for 10 minutes at 160° yielded only the starting sulfanilamide.

Attempted Reaction of N^1-(2-pyridyl)-N^4-Benzhydrylsulfanilamide with benzhydrol. Fusion of 1 g. (0.002 mole) of N^1-(2-pyridyl)-N^4-benzhydrylsulfanilamide with 0.49 g. (0.002 mole) of benzhydrol was carried out in the presence of 0.5 g. (0.003 mole) of zinc chloride for 20 minutes at 180°. Treatment with ethanol yielded a product, which, when recrystallized twice from acetone-water melted at 232-234°. A mixed melting point with N^1-(2-pyridyl)-N^4,3-Dibenzhydrylsulfanilamide showed no depression.

N^1-(2-pyrimidyl)-N^4,3-dibenzhydrylsulfanilamide was prepared by fusing 2.2 g. (0.005 mole) of benzhydrol and 1.8 g. (0.01 mole) of sulfadiazine in the presence of 1.36 g. (0.01 mole) of zinc chloride, at 150° for 5 minutes. Treatment of the cooled reaction mixture with ethanol yielded the title compound, which, when recrystallized twice from an acetone-water mixture, melted at 249-250°.

Calc. for $C_{36}H_{30}N_4O_2S$: C, 74.20; H, 5.19; N, 9.62.

Found: C, 74.24; H, 5.22; N, 9.48.

The infrared spectrum displayed a single amino stretching vibration at 3367 cm^{-1}. The SO_2 symmetric stretching vibration appeared at 1163 cm^{-1}.

Similar fusions at higher temperatures (175-185°), for the same length of time afforded unresolvable gums.

N^1-(2-pyrimidyl)-3,5-dibromosulfanilamide was prepared using the procedure previously described for the bromination of N^1-p-Benzhydrylphenyl)-3-benzhydrylsulfanilamide (compound no. 13d). Two recrystallizations from ethanol gave the title compound melting at 214-216°. Lit. m.p. 215° (77).

Attempted Reaction of N^1-(2-pyrimidyl)-3,5-dibromosulfanilamide with Benzhydrol.

A mixture of benzhydrol 1.0 g. (0.005 mole), N^1-(2-pyrimidyl)-3,5-dibromosulfanilamide 1.3 g. (0.005 mole) and zinc chloride 0.7 g. (0.005 mole) was fused at 150° for 10 minutes. On treatment of the cooled reaction mixture with ethanol, an adhesive gum resulted. Attempts at crystallizing the gummy material failed.

N^1-(p-Benzhydrylphenyl)-N^4-benzhydrylsulfanilamide

Fusion of 2.0 g. (0.008 mole) of sulfanilanilide with 3.0 g. (0.016 mole) of benzhydrol in the presence of 2.14 g. (0.016 mole) of zinc chloride for 2 minutes at 130° yielded a gummy residue. Upon extraction with chloroform, and recrystallization from ethanol, the title compound, melting at 215-216° was isolated. A mixed melting point determination with an authentic sample of the title compound, prepared earlier (compound 13d'), showed no depression.

N^1-(2-Quinoxalinyl)-N^4-benzhydrylsulfanilamide. Fusion of 1.0 g. (0.003 mole) of sulfaquinoxaline with 1.2 g. (0.006

mole) of benzhydrol and 0.8 g. (0.006 mole) of zinc chloride according to the procedure of Giraud (44) yielded an unresolvable gum. Similarly, fusion at 180° for 45 minutes produced an unresolvable gum. However, fusion at 130° for 10 minutes yielded a yellow precipitate, which, when recrystallized from an acetone-water mixture, melted at 223-225°. A mixed melting point determination with an authentic sample of the title compound, prepared earlier (compound no. 12), showed no depression.

N^1-(4-Methyl-2-pyrimidyl)-N^4-benzhydrylsulfanilamide

Fusion of 1.0 g. (0.004 mole) of sulfamerazine with 1.4 g. (0.008 mole) of benzhydrol in the presence of 1.0 g. (0.008 mole) of zinc chloride, by the method used for the reaction of p-toluidine, mentioned earlier, yielded a gum which could not be crystallized. However, fusion at 130° for 7 minutes yielded a white product which after several recrystallizations from an acetone-water mixture melted at 253-254°. A mixed melting point determination with an authentic sample of the title compound, prepared earlier (compound no. 4), showed no depression.

N^1-(5-Methyl-1,3,4-thiadiazole-2-yl)-N^4-benzhydrylsulfanilamide.

Fusion of 1.0 g. (0.004 mole) of sulfamethizole with 1.5 g. (0.008 mole) of benzhydrol in the presence of 1.0 g. (0.008 mole) of zinc chloride according to Giraud's procedure (44) yielded an unresolvable gum. Fusion at 130° for 5 minutes yielded a white product when the residue was stirred with ethanol. After recrystallization from chloroform-hexane, the product melted

at 214-215.5°. A mixed melting point determination with an authentic sample of the title compound, obtained earlier (compound no. 6), showed no depression.

Fusion Reactions of Sulfanilamide and Benzhydrol

(a) 3,5-Dibenzhydrylsulfanilamide. Fusion of 2.2 g. (0.012 mole) of benzhydrol and 1.0 g. (0.006 mole) of sulfanilamide in the presence of 1.6 g. (0.012 mole) of zinc chloride for 30 minutes at 180° yielded a pasty material. On cooling and stirring with ethanol , the title compound was isolated which melted at 296-297°.

Calc. for $C_{32}H_{28}N_2O_2S$: C, 76.16; H, 5.59; N, 5.55.

Found: C, 76.25; H, 5.81; N, 5.35.

The infrared spectrum displayed three peaks at 3378, 3300 and 3205 cm^{-1}.

Fusion of a mixture containing a three-to-one, or a five-to-one molar ratio of the alcohol and zinc chloride to sulfanilamide also yielded the title compound.

(b) N^4,N^1,3-Tribenzhydrylsulfanilamide. Fusion of 3.0 g. (0.016 mole) of benzhydrol and 1.0 g. (0.006 mole) of sulfanilamide in the presence of 2.2 g. (0.016 mole) of zinc chloride for 5 minutes at 100° yielded a white product after stirring the residue with ethanol. After two recrystallizations from dioxane-water, the title compound, melting at 206°-208° was obtained. A mixed melting point determination with an authentic sample of the title compound prepared earlier (compound 1t), gave no depression.

(c) N^1,3,5-Tribenzhydrylsulfanilamide and 3,5-dibenzhydrylsulfanilamide. Fusion of 3.0 g. (0.016 mole) of benzhydrol and 1.0 g. (0.006 mole) of sulfanilamide in the presence of 2.2 g. (0.016 mole) of zinc chloride at 160° for 3 minutes followed by stirring in ethanol, yielded a white product. After several recrystallizations from ethanol the compound melted at 296°. A mixed melting point determination with an authentic sample of 3,5-dibenzhydrylsulfanilamide, obtained earlier, showed no depression. The remainder of the solution was concentrated and the gummy residue was extracted with chloroform. Upon evaporation of the chloroform a gummy material was again isolated. However, stirring the gum in the ethanol yielded a white precipitate, which after several recrystallizations from ethanol melted at 193°-194.5°.

Calc. for $C_{45}H_{38}N_2O_2S$: C, 80.56; H, 5.71; N, 4.18.

Found: C, 80.69; H, 5.78; N, 4.42.

The infrared spectrum displayed two bands in the amino stretching region at 3390 cm^{-1} and 3300 cm^{-1}.

(d) 3,5-dibenzhydrylsulfanilamide. 1.0 g. (0.002 mole) of N^4,N^1,3-Tribenzhydrylsulfanilamide, 0.5 g. (0.004 mole) of zinc chloride and 0.5 g. (.003 mole) of sulfanilamide were fused at 190° for 10 minutes, then cooled and stirred with alcohol. A white product formed which when recrystallized twice from an acetone-water mixture melted at 296°. No depression of the melting point was observed when a mixed melting point determination was done with an authentic sample of the title compound.

(e) 3,5-Dibenzhydrylsulfanilamide. The reaction (d) above was duplicated, however, the 0.5 g. of sulfanilamide was replaced by 0.5 g. of naphthalene. The product isolated failed to depress the melting point of an authentic sample of the title compound.

(f) 3,5-Dibenzhydrylsulfanilamide. 1.0 g. (0.003 mole) of N^4-benzhydrylsulfanilamide, 0.4 g. (0.003 mole) of zinc chloride and 0.5 g. (0.003 mole) of sulfanilamide were heated at 210°. At this temperature the material was not in a liquid state. On heating at this temperature for 15 minutes, then cooling the reaction to room temperature, then stirring with ethanol, a white product resulted. Recrystallization from alcohol yielded a compound melting at 296°. A mixed melting point determination with an authentic sample of the title compound showed no depression.

Attempted Fusions of the Remaining Sulfanilamides with Benzhydrol

The remainder of the sulfanilamides in this study were reacted with benzhydrol according to Giraud's procedure (44), however, only gums were isolated and attempts to crystallize these failed. Modifications of the procedure, such as increasing or decreasing the reaction times, the reaction temperatures, the amount of catalyst or various combinations of these variables, similarly yielded unresolvable gums.

N^1-Xanthenyl-3,5-dibenzhydrylsulfanilamide was prepared by reacting 3,5-dibenzhydrylsulfanilamide with xanthydrol by the

general procedure described earlier. The product isolated was recrystallized from an acetone-water mixture several times, yielding the title compound melting at 207°-208°.

Calc. for $C_{45}H_{36}N_2O_2S$: C, 78.92; H, 5.30; N, 4.09,

Found: C, 78.38; H, 5.31; N, 4.40.

This compound could not be further purified.

The infrared spectrum displayed two bands and a shoulder at 3356, 3249 and 3289 cm^{-1}, respectively.

N^1,3,5-Tribenzhydrylsulfanilamide

A solution containing 2.0 g. (0.004 mole) of 3,5-dibenzhydrylsulfanilamide, 0.73 g. (0.004 mole) of benzhydrol and 6 drops of 70% perchloric acid was refluxed in 15 ml. of nitromethane for 20 minutes. The reaction became very dark brown in color after this time. Upon cooling and concentration in vacuo of the reaction mixture, a viscous gum was recovered. Stirring the gum in alcohol caused a precipitate of a solid white material. The compound, upon recrystallization twice from ethanol, melted at 193°-194°. A mixed melting point determination with an authentic sample of the title compound isolated previously, failed to show any depression.

The Reaction of Compounds Related to the Sulfanilamides

Reactions of p-Aminobenzoic Acid with Benzhydrol

(a) N-Benzhydryl-p-Aminobenzoic Acid

Heating 1.0 g. (.007 mole) of p-aminobenzoic acid and 1.0 g. (.007 mole) of benzhydrol in the presence of 3 drops of perchloric acid for 20 minutes at 75° yielded a white material, which when

recrystallized three times from ethanol, melted at 201°-202.5°.

Calc. for $C_{20}H_{17}NO_2$: C, 79.18; H, 5.65; N, 4.62.

Found: C, 79.23; H, 5.46; N, 4.85.

The infrared spectrum displayed a single peak in the amino stretching region at 3390 cm^{-1}.

(b) 2,6-Dibenzhydrylaniline

Heating 2.0 g. (0.015 mole) of benzhydrol, 1.0 g. (0.007 mole) of p-aminobenzoic acid and 8 drops of 70% perchloric acid in 15 ml. of nitromethane for 45 minutes following the general procedure, yielded a white product. The compound, after two recrystallizations from ethanol, melted at 175°-176°. A mixed melting point with an authentic sample of the title compound, prepared earlier, showed no depression.

(c) N,3-Dibenzhydryl-p-aminobenzoic acid

The reaction (b) above was duplicated, however, the reaction was allowed to proceed for only 4 minutes at reflux temperature. Cooling the reaction mixture to room temperature afforded a white precipitate which, after two recrystallizations from an acetone-water mixture melted at 247°-248°.

Calc. for $C_{33}H_{27}NO_2$: C, 84.40; H, 5.78; N, 3.00.

Found: C, 83.34; H, 5.78; N, 2.98.

This compound cound not be purified further.

The infrared spectrum displayed a single amino stretching vibration at 3333 cm^{-1}. A strong carbonyl absorption was also present at 1665 cm^{-1}.

(d) 2,6-Dibenzhydrylaniline

Concentration of the remaining nitromethane solution from (c) above, in vacuo, yielded a gummy product. Extraction with chloroform and recrystallization from ethanol yielded a compound melting at 175°-176°. A mixed melting point determination with an authentic sample of the title compound showed no depression.

(e) 2,6-Dibenzhydrylaniline

Fusion of 1.0 g. (0.007 mole) of p-aminobenzoic acid and 2.0 g. (0.015 mole) of benzhydrol in the presence of 1.8 g. (0.015 mole) of zinc chloride at 150° for 45 minutes, cooling, then stirring with ethanol afforded the title compound. After two recrystallizations from ethanol the compound melted at 174°-175°. A mixed melting point determination with an authentic sample of the title compound showed no depression.

The Reaction of m-Aminobenzoic Acid with Benzhydrol

(a) N,4-Dibenzhydryl-3-aminobenzoic acid

The reaction of 2.0 g. (0.015 mole) of benzhydrol, 1.0 g. (0.007 mole) of m-aminobenzoic acid and 8 drops of 70% perchloric acid in 15 ml. of nitromethane was performed according to the general procedure given earlier. The title compound was isolated, which melted at 203°-204° after three recrystallizations from ethanol.

Calc. for $C_{33}H_{27}NO_2$: C, 84.58; H, 5.80; N, 2.98.

Found: C, 84.58; H, 5.69; N, 3.12.

The infrared spectrum of this compound displayed a single amino stretching peak at 3333 cm^{-1} and a strong absorption was also present at 1681 cm^{-1}.

(b) Attempted Fusion of m-aminobenzoic acid with benzhydrol

Fusing 2.0 g. (0.015 mole) of benzhydrol and 1.0 g. (0.007 mole) of m-aminobenzoic acid in the presence of 1.8 g. (0.015 mole) of zinc chloride at 150° for 10 minutes yielded a viscous gum after stirring with ethanol. Repeated attempts at crystallizing the gum failed.

The Reactions of Metachloridine with Benzhydrol

(a) N^3-Benzhydryl-N^1-(5-chloro-2-pyrimidyl)metanilamide

Heating .75 g. (0.004 mole) of benzhydrol, 1.0 g. (0.004 mole) of metachloridine and 10 drops of 70% perchloric acid in 10 ml. of nitromethane, for 10 minutes at 80° yielded a product melting at 231°-232°, after three recrystallizations from an acetone-water mixture.

Calc. for $C_{23}H_{19}ClN_4O_2S$: C, 61.26; H, 4.25; N, 12.03.

Found: C, 61.53; H, 4.69; N, 12.04.

The infrared spectrum displayed a single amino stretching vibration at 3289 cm^{-1}. The SO_2 symmetric stretching vibration appeared at 1156 cm^{-1}.

(b) N^3-4-Dibenzhydryl-N^1-(5-chloro-2-pyrimidyl)metanilamide

The reaction of 1.5 g. (0.008 mole) of benzhydrol, 1.0 g. (0.004 mole) of metachloridine, and 10 drops of 70%

perchloric acid in 10 ml. of nitromethane, according to the general procedure, yielded a product which after four recrystallizations from an acetone-water mixture melted at 237°-240°.

Calc. for $C_{36}H_{29}ClN_4O_2S$: C, 70.06; H, 4.74; N, 9.08

Found: C, 70.25; H, 4.83; N, 9.04

The infrared spectrum displayed a single amino stretching signal at 3390 cm^{-1} and an SO_2 symmetric stretching vibration at 1149 cm^{-1}.

Antibacterial Evaluation Studies

Two four-inch petri dishes were filled with Bacto Hinton-Muller medium to a depth of about one-half inch. On solidification of the medium, the surfaces were inoculated, one with E. coli, the other with S. aureus, and spread uniformly. Approximately 1-10 mg. of the test sample, in the crystalline state, was placed onto the surface of the medium by means of a microspatula, keeping the sample in an area about one-half inch in diameter. The plates, each containing about six different samples of benzhydrylsulfanilamides were then placed in an incubator at 37°C for 48 hours. The plates were examined every 12 hours to determine if growth was inhibited in the area adjacent to the test samples.

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